IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	:	Sankyo Co. Ltd.
Patent Number	:	4,486,425
Issue Date	:	4 December 1984
Patent Title	:	*7-[2-(2-Aminothiazol-4-yl)-2-(Syn)-Methoxyiminoacetamido]-3-Methoxymethyl-3-Cephem-4-Carboxylates*

Commissioner of Patents and Trademarks
Box Patent Extension
Washington, DC 20231

APPLICATION FOR EXTENSION OF PATENT TERM

UNDER 35 USC 156 and 37 CFR 1.740

Sir:

Your Applicant, Sankyo Company Limited, represents that it is the Assignee of the entire interest in and to United States Patent No. 4,486,425 granted to Hideo Nakao, Koichi Fujimoto, Sadao Ishihara, Shinichi Sugawara, Isamu Igarashi on the 4th day of December 1984 for 7-[2-(2-Aminothiazol-4-yl)-2-(Syn)-Methoxyiminoacetamido]-3-Methoxymethyl-3-Cephem-4-Carboxylates. Your Applicant, acting through its duly authorized Agent, The Upjohn Company and the undersigned attorney, hereby submits this application for extension of patent term under 35 USC 156 by submitting the following information required by 37 CFR 1.740. A telefax copy of the Authorization of Agent and Power of Attorney evidencing the appointment of The Upjohn Company and the undersigned as duly appointed Agent is attached hereto as Appendix A. Originals of this document and Appendix F will be forwarded upon their receipt from Japan.

1. Identification of Approved Product

The approved product is cefpodoxime proxetil, the active ingredient in the drugs VANTIN Tablets, VANTIN Oral Suspension, BANAN Tablets, and BANAN Oral Suspension. Cefpodoxime proxetil is a chemical compound otherwise known as [6R-[6α,7β(Z)]]-7-[[(2-Amino-4-thiazolyl)(methoxyimino)acetyl]amino]-3-(methoxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid 1-[[(1-methylethoxy)carbonyl]oxy]ethyl ester.

2. Federal Statute and Applicable Provision Under Which Regulatory Approval Occurred.

Section 507 of the Federal Food, Drug and Cosmetic Act (21 USC 357; FDC Act)

3. Date Permission Received For Commercial Marketing and Use.

The first received permission for commercial marketing and use of cefpodoxime proxetil under Section 507 of the Federal Food, Drug and Cosmetic Act (21 USC 357) was on 7 August 1992, the date on which the four drugs identified under paragraph (1) above received simultaneous approval.

4. Identification of Active Ingredient in Drug Product and Statement That It has Not Been Previously Approved For Commercial Marketing or Use Under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act or the Virus-Serum-Toxic Act.

The sole active ingredient of VANTIN Tablets, VANTIN Oral Suspension, BANAN Tablets and BANAN Oral Suspension is cefpodoxime proxetil. Cefpodoxime proxetil has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

5. A. Statement That the Application Is Being Submitted Within the 60-Day Period Permitted For Submission and the Last Day On Which the Application Can Be Submitted.

While this application for patent term extension is not being submitted within sixty (60) days of the date cefpodoxime proxetil received permission for marketing as required under 37 CFR 1.720(f), Applicant nonetheless requests that this application be considered as timely filed since the failure to file within sixty (60) days was unintentional. Thus Applicant requests that the 60 day period referred to in 35 USC 156(d)(1) be interpreted by the Commissioner as commencing on the date that the Applicant first became aware of an unintentional failure to file such application. Attached as Appendix F is a supporting declaration setting forth the circumstances under which the Applicant first became aware of the unintentional failure to file. Since Applicant first became aware of the unintentional error on 4 December 1992, Applicant requests an interpretation that the last day for submission of this application for extension be 2 February 1993.

B. Argument in Support of Submission Date

Public policy supports the remedial interpretation of the duration of the 60 day period as requested by Applicant. Congress has twice in the last decade (PL 97-247 (1982) and PL 102-444 (1992)) amended the patent law to remediate unintentional failures to act. Thus, one can now revive applications which become unintentionally abandoned because of a failure to respond to the PTO or to pay a fee during the period prescribed by statute. (See 35 USC 41(a)(7).) Similarly, 41 USC 41 (c)(1) has recently been amended in the last Congress to permit the payment of maintenance fees up to two years late. While

Unimed V. Quigg, 888 F. 2d 826 (Fed. Cir. 1989) stated that the language in 35 USC 156(d)(1) "on the date the product received permission under the provision of law under which the regulatory review period occurred" meant the FDA approval date, the decision was before the latest statement from Congress evincing a remedial approach to such matters, and involved different facts than those herein. Moreover, the Patent Term Restoration Act is remedial in nature and therefore ought to be broadly construed to achieve Congress' intent. See, also, the reissue statute, 35 U.S.C. 251, which broadly allows for the correction of unintentional errors as well.

As far as the public is concerned, the interpretation Applicant requests will clearly not prejudice anyone, since the extension issue will be resolved well before the patent would otherwise expire, and certainly it would not be as prejudicial as reviving a patent two years after a maintenance fee has not been paid.

For all of the foregoing reasons, Applicant requests this application be treated as timely filed.

6. Identification of Patent For Which Extension Is Being Sought.

Patent No.	:	4,486,425
Name of Inventors	:	Hideo Nakao, Koichi Fujimoto, Sadao Ishihara, Shinichi Sugawara, Isamu Igarashi
Issue Date	:	4 December 1984
Expiration Date	:	4 December 2001

7. Copy of Patent

A copy of the patent identified in paragraph 6 hereof is attached as Appendix B.

8. Copies of Disclaimers, Certificates of Correction, Receipt of Maintenance Fee Payments and Re-examination Certificates.

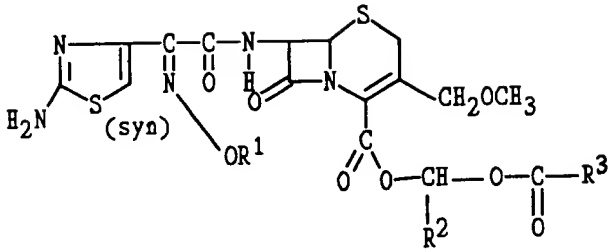
No disclaimers have been made regarding this patent. A certificate of correction has issued on 24 September 1985, and all maintenance fees that were due have been paid. A copy of the Certificate of Correction and the receipts for the maintenance fee payments in this case are attached as Appendix E.

9. Statement That Patent Claims the Approved Product or Method of Using the approved Product and Demonstration That Applicable Patent Claims Read on the Approved and Methods of Use.

U.S. Patent 4,486,425 claims the active ingredient of the approved product, cefpodoxime proxetil. Claim 1 is the applicable claim.

Claim 1 reads as follows:

A compound of the formula



wherein

R^1 is methyl;

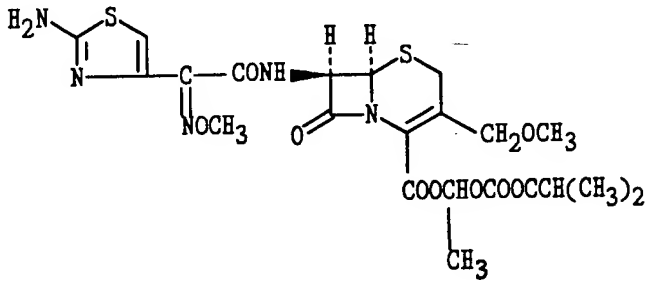
R^2 is hydrogen or methyl;

and

R^3 is a C_1-C_4 alkoxy;

and pharmaceutically acceptable acid addition salts thereof.

The structure of cefpodoxime proxetil is



Cefpodoxime proxetil falls within the scope of this Claim 1 when R^2 is methyl and R^3 is isopropoxy. Claims 3, 4, 5 and 6 also read on cefpodoxime proxetil as they contain these limitations, and Claim 6 is drawn specifically to it. Similarly, cefpodoxime proxetil falls within the scope of corresponding pharmaceutical composition claims 7, 9, 10, 11 and 12, which are correspondingly identical in scope to claims 1, 3, 4, 5 and 6.

10. Relevant Dates During Regulatory Review

Relevant dates and information pursuant to 35 USC 156(g) to enable the Examiner of Health and Human Services to determine the applicable regulatory review period are as follows:

The investigational new drug application, INDA No. 30,254, for cefpodoxime proxetil in tablets, was filed on 2 July 1987. August 2, 1987 was the earliest date upon which clinical trials could begin. The IND for the granules is 33,641.

The new drug application, NDA 50-674, for cefpodoxime proxetil was filed on 30 March 1991.

The new drug application, NDA 50-674, for cefpodoxime proxetil was approved for marketing in the United States on 7 August 1992.

The NDA for VANTIN Oral Suspension is NDA 50-675.

The NDA for BANAN Tablets is 50-687.

The NDA for BANAN Oral Suspension is 50-688.

The NDA filing dates for BANAN Tablets and BANAN Oral Suspension were approximately one week after the VANTIN dates, as Sankyo filed a letter of reference to the corresponding VANTIN files shortly after the NDA's for VANTIN Tablets and VANTIN Oral Suspension were filed.

11. Brief Description of Activities Undertaken By Applicant During the Applicable Regulatory Period With Respect to the Approved Product and the Significant Dates Applicable to Such Activities.

A brief description of the activities undertaken by Upjohn and Sankyo Company Limited, Applicant's licensor during the applicable regulatory review period with respect to cefpodoxime and the significant dates applicable to such activities is attached herewith as Appendix C and is a chronology of major communications between Applicant's licensees and the FDA from July 2, 1987, to August 7, 1992, and also includes some communications after that date.

Applicant is authorized by Upjohn to utilize the regulatory review period incurred by Upjohn and the NDA approval granted thereon to Upjohn as the basis of this application for the extension of the patent term of U.S. Patent 4,486,425.

The product names for VANTIN Tablets and VANTIN Oral Suspension were originally DOXEF Tablets and DOXEF Oral Suspension, respectfully, and were changed at the request of the FDA.

12. Applicant's Opinion as to Why the Patent is Eligible for Patent Extension and How the Length of Extension was Determined.

Applicant believes that U.S. Patent No. 4,486,425 is eligible for an extension under 35 USC 156 because it satisfies all of the requirements for such extension including, *inter alia*, the following:

(a) 35 USC 156(a):

U.S. Patent No. 4,486,425 claims a product in the sense that the "product" is a "human drug product" which is defined by the statute [35 USC 156(f)(2) and PTO Rules 37 CFR 7.710(b)(1)] to mean active ingredient of a new drug, i.e., cefpodoxime proxetil;

(b) 35 USC 156(a)(1):

The term of U.S. Patent No. 4,486,425 has not expired prior to submission of the application for extension;

(c) 35 USC 156(a)(2) and 37 CFR 1.720(b):

The term of U.S. Patent No. 4,486,425 has never been extended;

(d) 35 USC 156(a)(3):

This application for extension is submitted by the duly authorized agent of the owner of record of U.S. Patent No. 4,486,425 in accordance with the requirements of 35 USC 156(d) and 37 CFR 1.710;

(e) 35 USC 156(a)(4):

The approved cefpodoxime proxetil containing products were subject to regulatory review prior to their commercial marketing or use;

(f) 35 USC 156(a)(5)(A):

The simultaneous permission for the commercial marketing or use of cefpodoxime proxetil in the four products noted above, after the regulatory review period, is the first permitted commercial marketing or use of cefpodoxime proxetil containing products under the provisions of the FDC Act (21 USC 355) under which such regulatory period matured;

(g) 35 USC 156(c)(4):

No other patent has been extended for the same regulatory review period for products containing cefpodoxime proxetil.

Length of Extension:

Applicant requests an extension of the term of US patent 4,486,425 of 1164 days, or 3.2 years, computed as follows:

(a) The regulatory review period under 35 USC 156(g)(1)(B) was from August 2, 1987, the date of the IND, to August 7, 1992, the date of NDA approval;

(b) The period of review under 35 USC 156(g)(1)(B)(i), hereinafter the IND period, was from August 2, 1987 (effective date of IND) until March 30, 1991 (NDA submission date), which is 1336 days or 3.66 years.

(c) The period of review under 35 USC 156(g)(1)(B)(ii), hereafter the NDA period, was from March 30, 1991 (NDA submission date) until August 7, 1992 (NDA approval date), which is 496 days or 1.35 years.

(d) The total regulatory review period under 35 USC 156(g)(1)(B) is 1832 days, or 5.0 years.

(e) Applicant and Sankyo acted with due diligence during the entire period of regulatory review and therefore the noted term of eligible extension under 35 USC 156(c) should not be shortened for lack of due diligence.

(f) Under 35 USC 156(c)(2) the period of extension includes only one-half of IND period determined under 35 USC 156(g)(1)(B)(i), i.e., 668 days or 1.83 years.

(g) In compliance with 35 USC 156(c)(3) the period remaining in the term of U.S. Patent No. 4,486,425 after NDA approval of cefpodoxime proxetil is 9 years 4 months, or 9.3 years. The period of extension, computed as half the IND period, and all of the NDA period, is 1164 days, or 3.2 years, which is less than 5 years as specified in 35 USC 156 (g)(6)(A), and the total of the extension and the period remaining in the term of the patent from the date of marketing approval does not exceed fourteen years, as required under 35 USC 156 (b)(3).

13. Acknowledgment of Duty of Disclosure.

Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination to be made relative to this application for extension.

14. Fee.

The prescribed fee for receiving and acting upon this application for extension to be charged the Applicant's account as authorized in the accompanying letter which is submitted in duplicate.

15. The Name, Address and Telephone Number of the Person to Whom Inquires and Correspondence Relating to the Application for Patent Term Extension are to be Directed:

Lawrence T. Welch
Corporate Intellectual Property Law
The Upjohn Company
301 Henrietta Street
Kalamazoo, MI 49001
Telephone: 616-385-7237

16. Certified Duplicate of Application.

A certified duplicate of this application is attached.

17. Declaration.

The declaration set forth in 37 CFR 1.740(b) for Patent Term Extension under 35 USC 156 is attached as Appendix D.

Respectfully submitted,

Date: 7 December 1992

Lawrence T. Welch, Attorney
Registration No. 29,487
Telephone: (616) 385-7237

Mailing Address: Corp. Intellectual Property Law, The Upjohn Company, Kalamazoo, MI 49001

APPENDIX A

Authorization of Agent and Power of Attorney
(Original to be Filed upon Receipt)

PATENT/Docket No. 4722 EX
U.S. Patent 4,486,425
Application for Extension
Appendix A-1

APPENDIX A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re	:	U.S. Patent 4,486,425
Issued	:	4 December 1984
To	:	Hideo Nakao, Koichi Fujimoto, Sadao Ishihara, Shinichi Sugawara, Isamu Igarashi
For	:	*7-[2-(2-Aminothiazol-4-yl)-2-(Syn)-Methoxyiminoacetamido]-3-Methoxymethyl-3-Cephem-4-Carboxylates*

Commissioner of Patents and Trademarks
Box Patent Extension
Washington, DC 20231

AUTHORIZATION OF AGENT AND POWER OF ATTORNEY

Sir:

Sankyo Co. Ltd., a corporation organized and existing under the laws of Japan and having its head office in Tokyo, Japan, being the owner of record of the above-identified U.S. Letters Patent, hereby authorize and appoint The Upjohn Company, a corporation organized and existing under the laws of Delaware and having its head office at 7000 Portage Road, Kalamazoo, Michigan 49001-0199, and the Attorneys named below:

Robert A. Armitage (Registration No. 27,417) and

Lawrence T. Welch (Registration No. 29,487)

all being employees of The Upjohn Company, individually and collectively to be the agents and attorneys of Sankyo Co. Ltd. with regard to an application for extension of the term of U.S. Patent 4,486,425 under 35 USC 156 and to transact all business in the U.S. Patent and Trademark Office in connection therewith.

PATENT/Docket No. 4722 EX
U.S. Patent 4,486,425
Application for Extension
Appendix A-2

Please address all communication in the above matter to:

Lawrence T. Welch
Registration No. 29,487
Corporate Intellectual Property Law
The Upjohn Company
Kalamazoo, Michigan 49001
(616) 385-7237

SANKYO CO. LTD.

By: Yoshibumi Kawamura
Name: Yoshibumi Kawamura
Title: Representative Director and President

Date: December 4, 1992

APPENDIX B

Copy of U.S. Patent 4,486,425

United States Patent [19]

Nakao et al.

[11] **Patent Number: 4,486,425**

[45] **Date of Patent: Dec. 4, 1984**

[54] **7-[2-(2-AMINOTHIAZOL-4-YL)-2-(SYN)-METHOXYIMINOACETAMIDO]-3-METHOXYMETHYL-3-CEPHEM-4-CARBOXYLATES**

[75] Inventors: **Hideo Nakao; Koichi Fujimoto; Sadao Ishihara; Shinichi Sugawara; Isamu Igarashi, all of Hiromachi, Japan**

[73] Assignee: **Sankyo Company Limited, Tokyo, Japan**

[21] Appl. No.: **304,988**

[22] Filed: **Sep. 23, 1981**

[30] **Foreign Application Priority Data**

Sep. 30, 1980 [JP] Japan 55-136449
Apr. 13, 1981 [JP] Japan 56-55231
Jun. 10, 1981 [JP] Japan 56-89116

[51] Int. Cl.³ A61K 31/545; C07D 501/34

[52] U.S. Cl. 424/246; 544/28; 544/29; 544/30

[58] Field of Search 424/246; 544/28

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,098,888 7/1978 Ochiai et al. 544/28
4,278,671 7/1981 Ochiai et al. 544/28
4,409,215 10/1983 Takaya et al. 424/246

FOREIGN PATENT DOCUMENTS

29557 6/1981 European Pat. Off. .
34536 8/1981 European Pat. Off. .

OTHER PUBLICATIONS

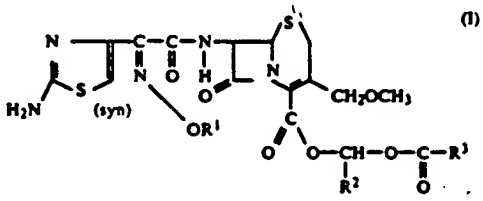
"Orally Active Esters of Cephalosporin Antibiotics. II Synthesis and Biological Properties of the Acetoxymethyl Ester of Cefamandole", Walter E. Wright et al., *The Journal of Antibiotics*, vol. XXXII, No. 11, Nov. 1979, pp. 1155–1160.

"Orally Active Esters of Cephalosporin Antibiotics. . . . ", W. J. Wheeler et al., Journal of Medicinal Chemistry, 1979, vol. 22, No. 6, pp. 657–661.

Primary Examiner—Paul M. Coughlan, Jr.
Attorney, Agent, or Firm—Frishauf, Holtz, Goodman & Woodward

[57] **ABSTRACT**

Compounds of formula (I):



(I)

wherein:

R^1 represents a lower alkyl group selected from methyl group and ethyl groups;

R^2 represents a hydrogen atom or a methyl group; and

R^3 represents a group selected from C_1–C_5 alkoxy groups,

and pharmaceutically acceptable acid addition salts thereof have valuable antibiotic activity and are suitable for oral administration. They may be prepared by a variety of synthetic routes.

12 Claims, No Drawings

7-[2-(2-AMINOTHIAZOL-4-YL)-2-(SYN)-METHOXYIMINOACETAMIDO]-3-METHOXYMETHYL-3-CEPHEM-4-CARBOXYLATES

The present invention relates to a series of new cephalosporin compounds which are particularly suitable for oral administration, to processes and intermediates for preparing these compounds and to compositions containing the compounds.

Although many cephalosporin derivatives which exhibit excellent antibacterial activity have been discovered, most of them are for parenteral administration. However, except where massive doses of an antibiotic are to be administered quickly, the preferred route of administration is oral, as oral preparations can be administered by the patient himself without the need for trained supervision or assistance. Unfortunately, of the many cephalosporin derivatives discovered, very few possess a combination of superior antibacterial activity, broad antibacterial spectrum against both gram-positive and gram-negative bacteria (especially against *Staphylococcus aureus*) and the ability to be absorbed efficiently through the digestive tract.

For example, cephalothin, cefazolin and cefmetazole are widely used for parenteral administration, particularly by injection. However, when these compounds are administered orally, only about 5% of the dose administered is recovered in the urine, showing their poor absorption through the digestive tract and their unsuitability for oral administration. This is thought to be due to the strong dissociation of the carboxy group at the 4-position (i.e. the low pKa value) and the strong acidity.

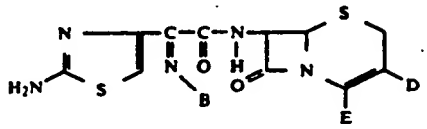
Because of this, many efforts have been made to improve the absorption of cephalosporin derivatives through the digestive tract by esterifying the 4-carboxy group but almost all such efforts have failed to obtain cephalosporin derivatives which are well absorbed through the digestive tract and which are therefore useful for oral administration, as described hereafter, in the one instance where absorption through the digestive tract has been significantly improved, the resulting compound lacks the desired broad antibacterial spectrum.

For example, the Journal of Antibiotics, 32 No. 11, 1155 (1979) discloses that the absorption of cefamandol through the digestive tract is not improved by esterification to prepare the acetoxymethyl ester, since this ester is only sparingly soluble in water. Although absorption of the ester through the digestive tract can be improved to a limited extent by administration of the ester in solution in certain organic solvents (such as propylene glycol), this is not a particularly good solution to the problem.

The Journal of Medicinal Chemistry, 22, 657 (1979), on the other hand, reports that the absorption through the digestive tract of another ester of a cephalosporin which is readily soluble in water, is not significantly improved due to chemical instability of the ester.

Furthermore, it is known that, in general, lower alkyl and benzhydryl esters of cephalosporins possess, in themselves, almost no antibacterial activity and that they are not hydrolyzed in vivo (which might otherwise convert them to an active acid) and hence they are not of value for therapeutic use, although they may be useful as synthetic intermediates.

Of the various cephalosporin derivatives known, one known class has a 2-(2-aminothiazol-4-yl)-2-alkoxyiminoacetamido group at the 7- position and may be represented by the following formula:



(in which B, D and E are substituents).

For example, Japanese Patent Application Kokai (i.e. as laid-open to public inspection) No. 149296/76 which corresponds to U.S. Pat. No. 4,098,888 discloses the following compounds:

(a) 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methyl-3-cephem-4-carboxylic acid;

(b) 3-acetoxymethyl-7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-cephem-4-carboxylic acid; and

(c) 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(1-methyl-1H-tetrazol-5-yl)thiomethyl-3-cephem-4-carboxylic acid.

We have discovered that the percentage recovery of these compounds in urine (which is a measure of their suitability for oral administration is only 3.2%, 1.5% and 2%, for compounds (a), (b) and (c), respectively; these compounds are, accordingly, unsuitable for oral administration.

Likewise, Japanese Patent Application Kokai No. 86188/81 published July 13, 1981 which corresponds to European Patent Application No. 29,557 published June 3, 1981 (both published after the Sept. 30, 1980 filing date of the priority Japanese Application No. 136449/1980) disclose. 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylic acid (d), which is the free carboxylic acid corresponding to certain of the compounds of the present invention. We have, however, found that the recovery rate in urine of compound (d) is only 5.5% and it is, therefore, unsuitable for oral administration. The Specification also discloses certain esters, particularly the t-butyl and benzhydryl esters, of cephalosporin compounds related to compound (d). However, as stated above, such esters are not believed to be readily convertible in vivo to the corresponding carboxylic acid and, as a result, may not be effective in actual use.

Japanese Patent Application Kokai No. 9296/79 which corresponds to U.S. Pat. No. 4,278,793 and 34795/78 which corresponds to U.S. Pat. No. 4,278,671 disclose the following pivaloyloxymethyl esters:

(e) pivaloyloxymethyl 3-acetoxymethyl-7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-cephem-4-carboxylate and

(f) pivaloyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(1-methyl-1H-tetrazol-5-yl)-thiomethyl-3-cephem-4-carboxylate.

We have also found that the recovery rate in urine of these compounds is only 8% and 14% for compounds (e) and (f), respectively, and these compounds also are unsuitable for oral administration.

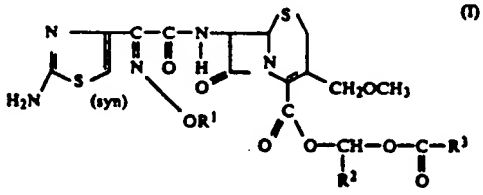
Comparing the recovery rates of compounds (a), (b) and (c) with the recovery rates of compounds (e) and (f), the results are rather surprising, since it is known that the absorption of ampicillin through the digestive tract is considerably improved by converting it to the pivaloyloxymethyl ester.

The above-mentioned Japanese Patent Application Kokai No. 34795/78 also discloses pivaloyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methyl-3-cephem-4-carboxylate, hereinafter referred to as "compound (g)". We have carried out extensive studies of this compound and have found that it exhibits very good recovery in urine, at a level almost comparable with that of the compounds of the present invention, thus suggesting that it may well be suitable for oral administration. However, as will be shown hereafter, compound (g), when administered orally, is hydrolyzed and converted in vivo to the corresponding carboxylic acid which, in turn, has poor activity against *Staphylococcus aureus*. Failure to inhibit the growth of this bacterium, which is perhaps one of the most important from the clinical point of view, could be a disadvantage in actual use.

It is, accordingly, clear from the above discussion that preparation of a cephalosporin derivative which meets the triple requirements of good absorption through the digestive tract, high antibacterial activity and a broad antibacterial spectrum, is not a simple matter. The cephalosporin nucleus includes many points at which different substituents may be introduced and the introduction of a particular substituent to improve one property may adversely affect other properties in a quite unpredictable way. Moreover, it has clearly been demonstrated that, even where a particular chemical modification is known to improve the properties of one particular compound (e.g. as with the preparation of the pivaloyloxymethyl ester to improve the absorption of ampicillin), this is not any indication that a similar modification will similarly improve the properties of any other compound.

We have now surprisingly discovered a limited class of cephalosporin derivatives which can be administered orally as they are readily absorbed through the digestive tract and which are then readily hydrolyzed and converted in vivo to the corresponding carboxylic acid which, in turn, shows quite outstanding activity against both gram-positive and gram-negative bacteria.

Accordingly, the present invention consists in compounds of formula (I):



(I)

in which:

R^1 represents a methyl group or an ethyl group,

R^2 represents a hydrogen atom or a methyl group; and

R^3 represents a C_1–C_5 alkyl or alkoxy group;

and pharmaceutically acceptable acid addition salts thereof.

The invention also provides a pharmaceutical composition comprising, as active ingredient, one or more of the compounds of the invention in admixture with a pharmaceutically acceptable carrier or diluent.

The invention also provides a variety of processes for preparing the compounds of the invention.

In the compounds of formula (I), when R^3 represents an alkyl group having from 1 to 5 carbon atoms, it is preferably a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl, isopentyl or t-pentyl group, most preferably a t-butyl group. R^3 most preferably represents an alkyl group having from 1 to 5 carbon atoms when R^2 represents a hydrogen atom.

When R^3 represents an alkoxy group having from 1 to 5 carbon atoms, it is preferably a methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, t-butoxy, pentyloxy or 1-ethylpropoxy group, most preferably an ethoxy group. R^3 most preferably represents an alkoxy group having from 1 to 5 carbon atoms when R^2 represents a methyl group.

Examples of compounds of the invention are given in the following list; the compounds are hereafter identified by the numbers assigned to them in the list.

1. Acetoxymethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate
2. Propionyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate
3. 1-Acetoxyethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate
4. Propionyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-ethoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate
5. Isopropionyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate
6. Butyryloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-ethoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate
7. 1-Propionyloxyethyl 7-[2-(2-aminothiazol-4-yl)-2-ethoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate
8. Isobutyryloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate
9. Pivaloyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate
10. Pivaloyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-ethoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate
11. Isovaleryloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate
12. 1-Pivaloyloxyethyl 7-[2-(2-aminothiazol-4-yl)-2-ethoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate
13. Methoxycarbonyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate
14. 1-Methoxycarbonyloxyethyl 7-[2-(2-aminothiazol-4-yl)-2-ethoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate
15. Ethoxycarbonyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate
16. 1-Ethoxycarbonyloxyethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate
17. 1-Ethoxycarbonyloxyethyl 7-[2-(2-aminothiazol-4-yl)-2-ethoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate

18. Propoxycarbonyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-ethoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate
19. 1-Isopropoxycarbonyloxyethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate
20. 1-Butoxycarbonyloxyethyl 7-[2-(2-aminothiazol-4-yl)-2-ethoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate.
21. Isobutoxycarbonyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate
22. 1-sec-Butoxycarbonyloxyethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate
23. 1-(1-Ethylpropoxycarbonyloxy)ethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate
24. 1-(1-Ethylpropoxycarbonyloxy)ethyl 7-[2-(2-aminothiazol-4-yl)-2-ethoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate
25. 3,3,3-Trimethylpropionyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate.

Of the compounds listed above, Compounds No. 9, 10, 16 and 17 are most preferred.

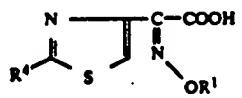
As indicated in the formula, the compounds of formula (I) of the present invention are in the synform which has been found to have much stronger antibacterial activity than the corresponding anti-isomers.

The compounds of formula (I) will form acid addition salts with various acids and the invention thus also includes such salts with pharmaceutically acceptable acids, for example inorganic acids (such as hydrochloric acid, sulphuric acid or phosphoric acid) or organic acids (such as methanesulphonic acid, benzenesulphonic acid or malonic acid). Of the acid addition salts, the hydrochlorides are most preferred.

The compounds of the present invention may be prepared by a number of methods, for example those described below.

Method 1

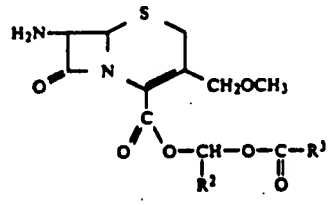
Compounds of formula (I) can be prepared by reacting a compound of formula (II):



(II)

(syn)

(in which R^4 represents an amino group or a protected amino group, and R^1 is as defined above) or a reactive derivative of said compound of formula (II) with a compound of formula (III):



(III)

(in which R^2 and R^3 are as defined above) and, if necessary, deprotecting the group R^4.

In the above compounds of formula (II), preferred amino-protecting groups included in R^4 are those groups which may readily be removed to restore a free amino group, for example the trityl, formyl, t-butoxycarbonyl or 2-ethoxycarbonyl-1-methylvinyl groups, which may be removed by treatment with an acid, the 2,2,2-trichloroethoxycarbonyl group, which may be removed by reduction, the 2-methanesulphonylethoxycarbonyl group, which may be removed by treatment with an alkali, or the chloroacetyl group, which may be removed by treatment with thiourea.

The carboxylic acid of formula (II) may itself be used in the free form or it may be used in the form of a reactive derivative. Suitable reactive derivatives include the acid halide, the acid anhydride, mixed acid anhydrides, reactive esters, reactive amides and the acid azide. Preferred mixed acid anhydrides include mixed acid anhydrides with mono-(lower alkyl)carbonates, such as monomethyl carbonate or monoisobutyl carbonate, and mixed acid anhydrides with lower alkanoic acids, such as pivalic acid or trichloroacetic acid. Preferred reactive esters include the p-nitrophenyl ester, the pentachlorophenyl ester and the N-hydroxyphthalimide ester.

Where the compound of formula (II) is employed in the form of the free acid, we prefer to carry out the reaction in the presence of a condensing agent. Examples of suitable condensing agents include: di-substituted carbodiimides, such as dicyclohexylcarbodiimide, imidazolides, such as carbonyldiimidazole or thionyldiimidazole; N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline, or a Vilsmeier reagent prepared from dimethylformamide and, for example, phosphorus oxychloride or thionyl chloride.

Where a reactive derivative of the acid (II) is employed, the use of such a condensing agent is not necessary; however, for certain reactive derivatives, it may be desirable to carry out the reaction in the presence of a base. Examples of suitable bases include: alkali metal compounds, such as sodium bicarbonate, potassium bicarbonate, sodium carbonate or potassium carbonate; or aliphatic, aromatic or nitrogen-containing heterocyclic bases, such as triethylamine, N,N-dimethylaniline, N,N-diethylaniline, N-methylpiperidine, N-methylpyrrolidine, pyridine, collidine or lutidine.

The reaction of the acid (II) or its reactive derivative with the compound of formula (III) is preferably effected in the presence of a solvent, the nature of which is not critical, provided that it has no adverse effect upon the reaction. Preferred solvents include inert organic solvents (such as acetone, methyl ethyl ketone, tetrahydrofuran, dioxan, ethyl acetate, chloroform, methylene chloride, acetonitrile, dimethylformamide or dimethylsulphoxide) or a mixture of such a solvent and water.

There is no particular limitation on the reaction temperature, but we normally prefer to conduct the reaction at ambient temperature or with cooling. The time required for the reaction will vary, depending mainly upon the method of acylation and the reaction temperature, but usually the reaction will require a period which may vary from several tens of minutes to several tens of hours.

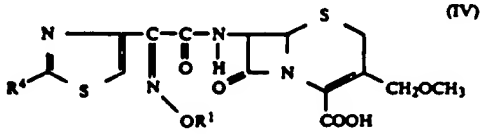
After completion of the reaction, the reaction product may be recovered from the reaction mixture by conventional means. For example, if a water-miscible

solvent is employed, the solvent is preferably removed by distillation under reduced pressure and the residue is dissolved in a water-immiscible solvent. The resulting solution is then washed with an acid and a base and dried, after which the solvent is distilled off to give the desired product. If a water-immiscible solvent is employed for the reaction, the reaction mixture is washed with an acid or a base and dried, after which the solvent is distilled off. The product thus obtained may, if necessary, be further purified by conventional means, for example by chromatographic techniques.

The reaction required to remove the protecting group, if R^4 represents a protected imino group, is, as mentioned above, conventional and will vary depending upon the particular protecting group chosen. After removal of the protecting group, the desired product may be recovered from the reaction mixture and purified, e.g. as suggested above, to give the desired compound of formula (I).

Method 2

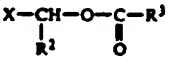
Compounds of formula (I) may be obtained by reacting a compound of formula (IV):



(IV)

(syn)

(in which R^1 and R^4 are as defined above) or a reactive derivative thereof with a compound of formula (V):



(V)

(in which X represents a halogen atom, such as a chlorine, bromine or iodine atom, preferably an iodine atom, and R^2 and R^3 are as defined above) and then, if necessary, deprotecting the group represented by R^4.

Preferred reactive derivatives of the compound of formula (IV) are salts, for example salts with a metal (such as sodium or potassium) or with an organic amine (such as triethylamine). Where the free acid (IV) is employed, the reaction is preferably effected in the presence of an acid-binding agent, which may be organic or inorganic, for example potassium carbonate, sodium carbonate, sodium bicarbonate, triethylamine, dicyclohexylamine, pyridine or N,N-dimethylaniline.

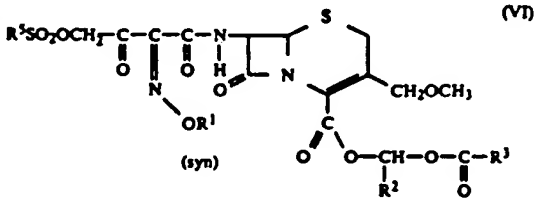
The reaction is preferably effected in the presence of a solvent, the nature of which is not critical, provided that it has no adverse effect upon the reaction. Suitable solvents include dimethylformamide, dimethylacetamide, dimethyl sulphoxide, hexamethylphosphoric triamide or acetonitrile, a mixture of two or more such solvent may be employed, as may a mixture of one or more of these solvents with one or more other inert organic solvents. The reaction may be effected over a wide range of temperatures, but we generally prefer to conduct it at ambient temperature or with cooling. The time required for the reaction may vary from a period of several minutes to several hours.

After completion of the reaction, the reaction mixture is preferably diluted with a water-immiscible solvent, washed successively with an aqueous solution of potassium bisulphate and an aqueous basic solution and then dried, after which the solvent is distilled off to give the desired product. This product may be further purified by conventional means, for example by chromatographic techniques.

Where R^4 represents a protected amino group, it may be converted to a free amino group as described in Method 1.

Method 3

Compounds of formula (I) may be obtained by reacting a compound of formula (VI):



(VI)

(syn)

(in which R^5 represents an alkyl group or an aryl group, and R^1, R^2 and R^3 are as defined above) with thiourea. Compounds of formula (VI) are new and themselves form part of the present invention.

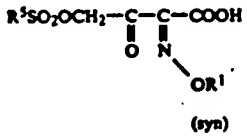
In the compounds of formula (VI), when R^5 represents an alkyl group, it is preferably an alkyl group having from 1 to 6 carbon atoms, for example a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl or hexyl group, more preferably a methyl or ethyl group. When R^5 represents an aryl group, it is preferably a substituted or unsubstituted phenyl or naphthyl group. In the case of substituted groups, there may be one or more substituents, normally from 1 to 5 substituents, and they may be the same or different. Suitable substituents include C_1–C_4 alkyl groups (e.g. methyl, ethyl, propyl, isopropyl or butyl), C_1–C_4 alkoxy groups (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy or isobutoxy) and halogen atoms (e.g. chlorine, bromine or fluorine atoms). The most preferred aryl groups represented by R^5 are the phenyl and p-methylphenyl groups.

Representative examples of compounds of formula (VI) include:

26. Acetoxymethyl 7-(2-methoxyimino-3-oxo-4-p-toluenesulphonyloxybutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate
27. 1-Acetoxyethyl 7-(2-ethoxyimino-3-oxo-4-p-toluenesulphonyloxybutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate
28. Propionyloxymethyl 7-(4-benzenesulphonyloxy-2-methoxyimino-3-oxobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate
29. 1-Propionyloxyethyl 7-(4-methanesulphonyloxy-2-methoxyimino-3-oxobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate
30. 1-Butyryloxyethyl 7-(4-ethanesulphonyloxy-2-ethoxyimino-3-oxobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate
31. Isobutyryloxymethyl 7-(2-methoxyimino-3-oxo-4-p-toluenesulphonyloxybutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate
32. Pivaloyloxymethyl 7-(2-methoxyimino-3-oxo-4-p-toluenesulphonyloxybutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate

33. Pivaloyloxymethyl 7-(2-ethoxyimino-3-oxo-4-p-toluenesulphonyloxybutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate
34. Pivaloyloxymethyl 7-(4-benzenesulphonyloxy-2-methoxyimino-3-oxobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate
35. Pivaloyloxymethyl 7-(4-methanesulphonyloxy-2-methoxyimino-3-oxobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate
36. Pivaloyloxymethyl 7-(4-ethanesulphonyloxy-2-ethoxyimino-3-oxobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate
37. 1-Pivaloyloxyethyl 7-(2-methoxyimino-3-oxo-4-p-toluenesulphonyloxybutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate
38. Methoxycarbonyloxymethyl 7-(4-methanesulphonyloxy-2-methoxyimino-3-oxobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate
39. Ethoxycarbonyloxymethyl 7-(4-benzenesulphonyloxy-2-ethoxyimino-3-oxobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate
40. 1-Ethoxycarbonyloxyethyl 7-(2-methoxyimino-3-oxo-4-p-toluenesulphonyloxybutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate
41. 1-Ethoxycarbonyloxyethyl 7-(4-methanesulphonyloxy-2-methoxyimino-3-oxobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate
42. 1-Ethoxycarbonyloxyethyl 7-(2-ethoxyimino-3-oxo-4-p-toluenesulphonyloxybutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate
43. Isopropoxycarbonyloxymethyl 7-(2-methoxyimino-3-oxo-4-p-toluc:. sulphonyloxybutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate.
44. 1-Butoxycarbonyloxyethyl 7-(4-benzenesulphonyloxy-2-methoxyimino-3-oxobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate
45. 1-(1-Ethylpropoxycarbonyloxy)ethyl 7-(2-methoxyimino-3-oxo-4-p-toluenesulphonyloxybutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate
46. 3,3,3-Trimethylpropionyloxymethyl 7-(2-methoxyimino-3-oxo-4-p-toluenesulphonyloxybutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate

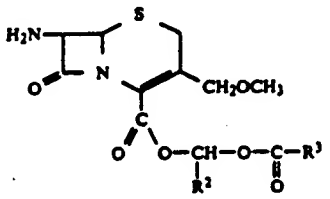
Compounds of formula (VI) may be prepared, for example, by reacting a compound of formula (VII):



(VII)

(syn)

(in which R^1 and R^5 are as defined above) or a reactive derivative thereof with a compound of formula (III):

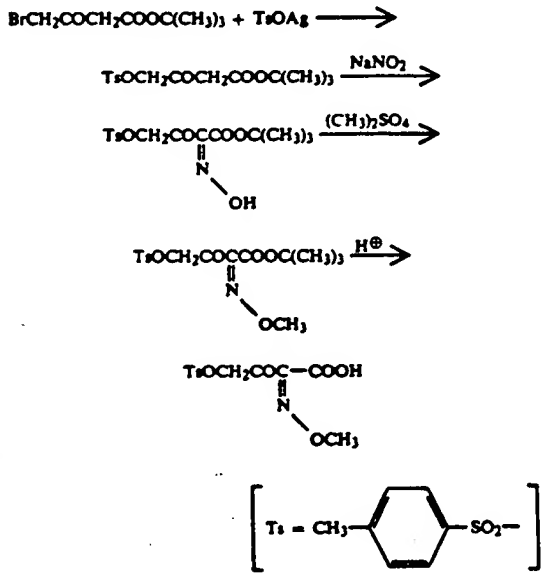


(III)

(in which R^2 and R^3 are as defined above). Compounds of formula (VII) are new and also part of the present invention. Representative examples of compounds of formula (VII) include:

47. 2-Methoxyimino-3-oxo-4-p-toluenesulphonyloxybutyric acid
48. 2-Ethoxyimino-3-oxo-4-p-toluenesulphonyloxybutyric acid
49. 4-Benzenesulphonyloxy-2-methoxyimino-3-oxobutyric acid
50. 4-Methanesulphonyloxy-2-methoxyimino-3-oxobutyric acid
51. 4-Ethanesulphonyloxy-2-ethoxyimino-3-oxobutyric acid.

Compounds of formula (VII) may, for example, be prepared by the series of reactions illustrated in the following reaction scheme for the preparation of the compound in which R^5 represents a p-tolyl group and R^3 represents a methyl group:



In the reaction to prepare the compound of formula (VI), the free acid or formula (VII) may be used as such or a reactive derivative of this free acid may be used. Where the free acid is used, the reaction is preferably carried out in the presence of a condensing agent, for example: a disubstituted carbodiimide, such as N,N'-dicyclohexylcarbodiimide; an azolide compound, such as N,N'-carbonylimidazole, a dehydrating agent, such as N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline, phosphorus oxychloride or an alkoxyacetylene; or a Vilsmeier reagent prepared from dimethylformamide and phosphorus oxychloride.

Where a reactive derivative of the acid of formula (VII) is employed, no such condensing agent is needed, but, depending upon the nature of the reactive derivative, the reaction may preferably be carried out in the presence of a base. Suitable bases include, for example: alkali metal compounds, such as sodium bicarbonate, potassium bicarbonate, sodium carbonate or potassium carbonate; and aliphatic, aromatic or nitrogen-containing heterocyclic bases, such as triethylamine, N,N-dimethylaniline, N,N-diethylaniline, N-methylpiperi-

dine, N-methylpyrrolidine, pyridine, collidine or lutidine.

Preferred reactive derivatives of the acid (VII) include the acid halide, the acid anhydride, mixed acid anhydrides, active esters, active amides and the acid azide. Suitable mixed acid anhydrides include those with monoesters of carbonic acid (for example monomethyl carbonate or monoisobutyl carbonate) and those with lower alkanoic acids or lower haloalkanoic acids (such as pivalic acid or trichloroacetic acid). Suitable active esters include, for example, the p-nitrophenyl ester, the pentachlorophenyl ester, the N-hydroxyphthalimide ester and the N-hydroxybenzotriazole ester.

The reaction is preferably effected in the presence of a solvent, the nature of which is not critical, provided that it has no adverse effect upon the reaction. Suitable solvents include acetone, tetrahydrofuran, dioxan, ethyl acetate, chloroform, methylene chloride, dimethylformamide, acetonitrile and water, as well as mixtures of two or more of these solvents.

The reaction temperature is not particularly critical and the reaction is therefore normally performed at room temperature or with cooling. The time required for the reaction will vary, depending mainly on the nature of the acylating agent and on the reaction temperature, but the reaction will normally be complete within from 10 minutes to several tens of hours.

Upon completion of the reaction, the desired compound of formula (VI) may be recovered from the reaction mixture by conventional means and, although the compound may, if necessary, be purified (for example by recrystallization or by the various chromatographic techniques) it may also be used, without intermediate purification or separation, for the next step, that is to say the preparation of the desired compound of formula (I).

The reaction to produce the compound of formula (I) comprises contacting the compound of formula (VI) with thiourea, preferably in the presence of a suitable solvent. The nature of the solvent is not critical, provided that it has no adverse effect upon the reaction. Suitable solvents include water, methanol, ethanol, dimethylformamide, dimethylacetamide, acetonitrile, tetrahydrofuran and mixtures of two or more of these solvents.

If desired, a base (such as sodium acetate or sodium bicarbonate) may be added to the reaction mixture in order to promote the reaction or assist it to go to completion. Formation of by-products may be prevented by effecting the reaction in the presence of a buffer solution of pH 6.5–7.

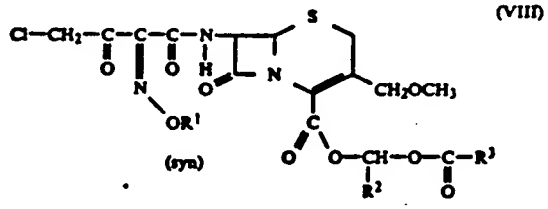
The amount of thiourea employed is preferably 1 or more equivalents per equivalent of said compound of formula (VI).

The reaction temperature is not particularly critical and the reaction is therefore preferably effected at ambient temperature. The time required for the reaction will vary, depending upon the reaction conditions, but a period of from several tens of minutes to several hours will generally be required.

Upon completion of the reaction, the desired compound of formula (I) may be recovered by conventional means, for example by concentration under reduced pressure, extraction, reprecipitation or chromatography.

Method 4

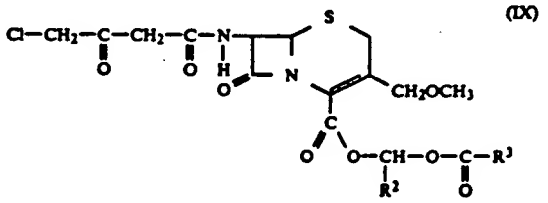
Compounds of formula (I) may also be obtained by reacting a compound of formula (VIII):



(VIII)

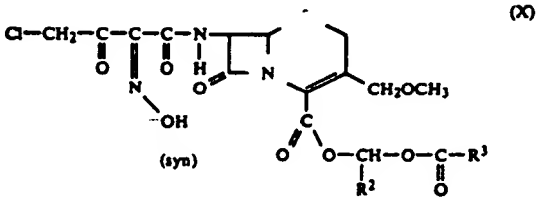
(in which R^1, R^2 and R^3 are as defined above) with thiourea.

Compounds of formula (VIII), which are new and also form part of the present invention, may be prepared by nitrosoating a compound of formula (IX):



(IX)

(in which R^2 and R^3 are as defined above) to give a compound of formula (X):



(X)

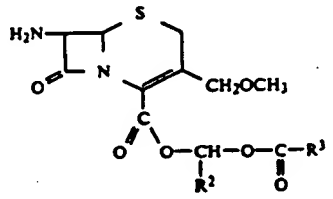
(in which R^2 and R^3 are as defined above) and then alkylating the hydroxy group attached to the imino nitrogen atom of said compound of formula (X).

Representative examples of the new compounds of formula (VIII) include:

52. Acetoxymethyl 7-(4-chloro-2-methoxyimino-3-oxobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate
53. 1-Acetoxyethyl 7-(4-chloro-2-methoxyimino-3-oxobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate
54. 1-Propionyloxymethyl 7-(4-chloro-2-methoxyimino-3-oxobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate
55. 1-Ethoxycarbonyloxyethyl 7-(4-chloro-2-methoxyimino-3-oxobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate
56. 1-Ethoxycarbonyloxyethyl 7-(4-chloro-2-ethoxyimino-3-oxobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate
57. Methoxycarbonyloxymethyl 7-(4-chloro-2-methoxyimino-3-oxobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate
58. Ethoxycarbonyloxymethyl 7-(4-chloro-2-ethoxyimino-3-oxobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate
59. Isopropoxycarbonyloxymethyl 7-(4-chloro-2-methoxyimino-3-oxobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate

60. Butoxycarbonyloxymethyl 7-(4-chloro-2-methoxyimino-3-oxobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate
61. 1-Propionyloxyethyl 7-(4-chloro-2-methoxyimino-3-oxobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate
62. 1-Butyryloxyethyl 7-(4-chloro-2-ethoxyimino-3-oxobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate
63. Isovaleryloxymethyl 7-(4-chloro-2-methoxyimino-3-oxobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate
64. Pivaloyloxymethyl 7-(4-chloro-2-methoxyimino-3-oxobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate
65. Pivaloyloxymethyl 7-(4-chloro-2-ethoxyimino-3-oxobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate
66. Isobutyryloxymethyl 7-(4-chloro-2-methoxyimino-3-oxobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate
67. 1-Pivaloyloxyethyl 7-(4-chloro-2-methoxyimino-3-oxobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate
68. 1-(1-Ethylpropoxycarbonyloxy)ethyl 7-(4-chloro-2-methoxyimino-3-oxobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate
69. 3,3,3-Trimethylpropionyloxymethyl 7-(4-chloro-2-methoxyimino-3-oxobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate.

The compound of formula (IX) can be prepared by acylating a compound of formula (III):



(III)

(in which R^2 and R^3 are as defined above) with 4-chloro-3-oxobutyryl chloride (which can be obtained by reacting diketene with chlorine). This acylation may be conducted by conventional means and is preferably effected in a solvent, the nature of which is not critical, provided that it has no adverse effect upon the reaction. Suitable solvents include methylene chloride, chloroform, tetrahydrofuran and dioxan. The acylation is preferably conducted in the presence of a base, preferably an organic base such as triethylamine, pyridine, N,N-dimethylaniline or N,N-diethylaniline. The reaction is preferably effected at about ambient temperature or at a lower temperature and will normally require a period of from several minutes to several hours. After completion of the reaction, the product of formula (IX) may be recovered and purified by conventional means, for example concentration, extraction with organic solvents, chromatographic techniques or recrystallization.

The nitrosoation of the compound of formula (IX) to prepare the compound of formula (X) may be effected by techniques known for the nitrosoation of reactive methylene groups. Such a nitrosoation reaction is normally effected using a metal salt of nitrous acid under acidic conditions or an ester of nitrous acid under suitable conditions. However, when preparing the compounds of the invention, it is necessary to carry out the reaction under such conditions that the cephalosporin ring system and the chlorine atom on the side chain at the 7-position do not participate in the reaction. It is, accordingly, desirable to carry out the reaction under weakly acidic or weakly basic conditions at a temperature below ambient. This reaction is normally carried out in the presence of a solvent, the nature of which is not critical, provided that it is capable of dissolving the compound of formula (IX) and does not have any adverse effect upon the reaction. Suitable solvents include formic acid, acetic acid, tetrahydrofuran, methanol, ethanol, chloroform, ethyl acetate and benzene, or a mixture of water with one or more of these solvents. The particular solvent chosen will depend upon the nature of the nitrosoating agent.

Examples of metal salts of nitrous acid employed as the nitrosoating agent include alkaline metal salts (such as sodium nitrite or potassium nitrite), preferably sodium nitrite. The nitrous acid ester is preferably an ester with a lower alcohol, for example pentyl nitrite or butyl nitrite.

Where a metal salt of nitrous acid is used as the nitrosoating agent, the reaction must be carried out under acidic conditions and, if an acidic solvent (such as formic acid or acetic acid) is not employed, the addition of an acid (which may be organic or inorganic) is necessary. Accordingly, we prefer to carry out the reaction using formic acid or acetic acid as the reaction solvent.

The reaction is preferably carried out at about ambient temperature or below and will require a period which may range from several minutes to several hours.

After completion of the reaction, the resulting product of formula (X) may be isolated and purified by conventional means, for example by concentration, extraction with organic solvents or chromatographic techniques.

The alkylation of the resulting compound of formula (X) to give the compound of formula (VIII) may be effected by reacting the compound of formula (X) with an alkylating agent, preferably in the presence of a solvent. The nature of the solvent is not critical, provided that it has no adverse effect upon the reaction. Suitable solvents include acetone, tetrahydrofuran, dioxan, methanol, ethanol, chloroform, ethyl acetate, diethyl ether and dimethylformamide, or a mixture of two or more of these solvents.

Suitable alkylating agents include dialkyl sulphates (e.g. dimethyl sulphate or diethyl sulphate), diazoalkanes (e.g. diazomethane) and alkyl halides (e.g. methyl iodide or ethyl iodide).

Except when a diazoalkane (such as diazomethane) is used as the alkylating agent, the reaction is preferably effected in the presence of a base. Suitable bases include: alkali metal carbonates, such as sodium carbonate or potassium carbonate; alkali metal hydroxides, such as sodium hydroxide or potassium hydroxide; and nitrogen-containing organic bases, such as triethylamine, pyridine or N,N-dimethylaniline.

The reaction is preferably effected at ambient temperature or below and will normally require a period of from several minutes to several hours. After completion of the reaction, the desired compound of formula (VIII) may be isolated and purified by conventional means, for example concentration, extraction with organic solvents, chromatographic techniques or recrystallization.

The reaction of the compound of formula (VIII) with thiourea to give the desired compound of formula (I) is essentially the synthesis of an aminothiazole derivative by reacting a haloketone with thiourea and may be carried out in much the same way as is common for this type of reaction.

The reaction is usually carried out in the presence of a solvent, the nature of which is not critical, provided that it has no adverse effect upon the reaction. The solvent is preferably an organic solvent (such as dimethylformamide, dimethylacetamide, methanol, ethanol or tetrahydrofuran) or a mixture of water with one or more of these organic solvents.

The thiourea is preferably employed in an amount of 1 or more equivalents per equivalent of said compound of formula (VIII).

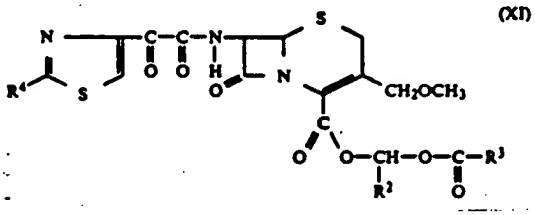
In order to accelerate the reaction, sodium iodide may be added to the reaction mixture and the hydrogen chloride formed in the reaction may be neutralized by the addition of a neutral phosphate buffer solution.

The reaction is preferably effected at ambient temperature and will normally be complete within a period of from 1 to 10 hours.

When the reaction is complete, the desired compound of formula (I) may be isolated and purified by conventional means, for example by concentration, extraction with organic solvents, chromatographic techniques, reprecipitation or recrystallization.

Method 5

Compounds of formula (I) may also be obtained by reacting a compound of formula (XI):



(XI)

(in which R^2, R^3 and R^4 are as defined above) with a compound of formula (XIII):

(XII)

(in which R^1 is as defined above) and then, if necessary, deprotecting the group represented by R^4.

Compounds of formula (XI) are new and also form part of the present invention. They may be prepared by reacting a compound of formula (XIII):

(XIII)

(in which R^4 is as defined above) or a reactive derivative thereof with a compound of formula (III).

Representative examples of the novel compounds of formula (XI) include:

70. Pivaloyloxymethyl 7-[2-(2-aminothiazol-4-yl)-glyoxylamido]-3-methoxymethyl-3-cephem-4-carboxylate
71. Pivaloyloxymethyl 7-[2-(2-formamidothiazol-4-yl)glyoxylamido]-3-methoxymethyl-3-cephem-4-carboxylate
72. 1-Ethoxycarbonyloxyethyl 7-[2-(2-aminothiazol-4-yl)glyoxylamido]-3-methoxymethyl-3-cephem-4-carboxylate
73. 1-Ethoxycarbonyloxyethyl 7-[2-(2-formamidothiazol-4-yl)glyoxylamido]-3-methoxymethyl-3-cephem-4-carboxylate.

In the reaction to produce the compound of formula (XI), the compound of formula (XIII) may be used either in the form of the free acid or in the form of a reactive derivative thereof. When the free acid is used, the reaction is preferably effected in the presence of a condensing agent, for example: a disubstituted carbodiimide, such as N,N'-dicyclohexylcarbodiimide, an imidazolide, such as N,N'-carbonylimidazole or thionyldiimidazole, N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline; or a Vilsmeier reagent prepared from dimethylformamide and phosphorus oxychloride or thionyl chloride.

On the other hand, where a reactive derivative of the acid (XIII) is employed, there is no need to use a condensing agent, but, depending upon the nature of the reactive derivative, it may be preferred to effect the reaction in the presence of a base. Suitable bases include: alkali metal compounds, such as sodium bicarbonate, potassium bicarbonate, sodium carbonate or potassium carbonate; and aliphatic, aromatic or nitrogen-containing heterocyclic bases, such as triethylamine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, pyridine, collidine or lutidine.

Reactive derivatives of the acid (XIII) include the acid halides, the acid anhydride, mixed acid anhydrides, active esters, active amides and the acid azide. Examples of suitable mixed acid anhydrides include those with monoesters of carbonic acid (for example monomethyl carbonate or monoisobutyl carbonate) and those with lower alkanoic acids and lower haloalkanoic acids (such as pivalic acid or trichloroacetic acid). Suitable active esters include, for example, the p-nitrophenyl ester, the pentachlorophenyl ester, the N-hydroxyphthalimide ester and the N-hydroxybenzotriazole ester.

The reaction is preferably effected in the presence of a solvent, the nature of which is not critical, provided that it has no adverse effect upon the reaction. Suitable solvents include acetone, methyl ethyl ketone, tetrahydrofuran, dioxan, ethyl acetate, chloroform, methylene chloride, dimethylformamide, acetonitrile and dimethyl sulphoxide, and mixtures of these solvents with water.

There is no particular limitation on the reaction temperature and accordingly the reaction is preferably effected at ambient temperature or with cooling. The time required for the reaction will vary, depending mainly on the nature of the acylating method and on the reaction temperature, but it will normally require a period of from 10 minutes to several tens of hours.

After completion of the reaction, the compound of formula (XI) may be recovered from the reaction mixture by conventional means and it may, if desired then be purified by conventional techniques such as chromatography.

The reaction of the compounds of formulae (XI) and (XII) is normally performed in a solvent, the nature of which is not critical, provided that it has no adverse effect upon the reaction. Suitable solvents include dimethylformamide, dimethylacetamide, acetonitrile and various alcohols, as well as mixtures of these solvents with water.

The alkoxyamine of formula (XII) is preferably employed in the form of a salt with an inorganic acid (such

as hydrochloric acid, nitric acid or sulphuric acid) or an organic acid (such as acetic acid or benzoic acid).

The reaction temperature is not critical, but we normally prefer to carry out the reaction at a temperature from ambient temperature to 60° C. The time required for the reaction may vary, depending upon the reaction conditions, but will generally be from 10 minutes to several hours.

After completion of the reaction, the desired compound of formula (I) may be recovered from the reaction mixture by conventional means, for example by adding water and a water-immiscible solvent (such as ethyl acetate) to the reaction mixture, separating the organic layer under slightly alkaline conditions from the aqueous layer and then removing the organic solvent by distillation from this organic layer to give the desired compound.

Where the group R^4 in the compound obtained by this process is a protected amino group, it may be deprotected using the techniques described in relation to Method 1.

The desired compound of formula (I) may, if necessary, be purified by conventional means such as recrystallization and/or chromatographic techniques.

The compounds of formula (I) and their acid addition salts may advantageously be employed in antibacterial compositions for oral administration. In order that a compound may be used for this purpose, it is essential, as mentioned above, that it should be well absorbed through the digestive tract after oral administration. Good absorption through the digestive tract is demonstrated by a good recovery of the compound or of degration products in the urine after oral administration.

The prior art compound (g) has a recovery rate in urine of 66.7%, which is very nearly comparable with the recovery rates of 75.9% and 78% of Compounds 5 and 6, which are representative of the compounds of the present invention. These figures are quite satisfactory for the purposes of oral administration.

However, in addition to this good absorption through the digestive tract, it is desirable that compounds such as the prior art compound (g) and the compounds of the invention should, after hydrolization in vivo, be very active against gram-positive and gram-negative bacteria. The compounds of the invention, as well as compound (g), are hydrolized in vivo to the corresponding carboxylic acids and hence it is the antibacterial activities of these carboxylic acids, rather than of the esters, which are important from the clinical point of view. The activities of the carboxylic acids corresponding to Compounds No. 5 and 6 and to compound (g) against various bacteria are shown in the following Table, in terms of their minimal inhibitory concentrations (μg/ml).

TABLE

	Compound 5	Compound 6	Compound (g)
Staphylococcus aureus 209P	0.4	0.2	12.5
Staphylococcus aureus 56	0.8	0.4	25
Escherichia coli NIHJ	0.4	0.8	0.8
Escherichia coli 609	0.4	0.8	0.8
Shigella flexneri 2a	0.8	0.4	0.8
Klebsiella pneumoniae 806	0.1	0.2	0.2
Klebsiella sp. 846	0.8	0.8	1.5
Proteus vulgaris	0.01	0.01	<0.1
Salmonella enteritidis G.	0.2	0.4	0.4

It is clear from the above Table, that the compounds of the invention and the prior art compound are all highly active against gram-negative bacteria, when administered orally. However, whereas Compounds 5 and 6 are active against *Staphylococcus aureus*, which is representative of the gram-positive bacteria, compound (g) has a rather low activity against these bacteria.

The compounds of the invention are preferably administered orally, for example in the form of capsules, tablets, powders, syrups or suspensions. The dosage depends upon the age, symptoms and body weight of the patient and on the duration of treatment, but the dosage may normally range from 0.2 g to 5 g per day, preferably from 0.5 g to 3 g per day for adults; however, if necessary, larger doses may be employed.

In the pharmaceutical compositions of the present invention, any conventional pharmaceutically acceptable carrier or diluent may be employed in admixture with the active compound or compounds. As the composition is generally intended to be administered orally, it is desirably presented in a form readily absorbed through the stomach or intestines. Tablets or capsules are normally in unit dosage form and may contain binding agents (e.g. syrup, gum arabic, gelatin, sorbitol, gum tragacanth or polyvinylpyrrolidone), diluents (e.g. lactose, sugar, corn starch, calcium phosphate, sorbitol or glycine), lubricants, (e.g. magnesium stearate, talc, polyethylene glycol or silica), disintegrating agents (e.g. potato starch) or wetting agents (e.g. sodium lauryl sulphate) or any combination thereof. The tablets may, if desired, be coated, e.g. with an enteric coating, as is well-known in the art.

Liquid formulations may be aqueous or oily suspensions, syrups, elixirs or similar compositions. Alternatively, the composition may be a dried product which can then be redissolved in water or another suitable vehicle before administration. Such liquid formulations may contain conventional additives, such as suspending agents (e.g. sorbitol syrup, methylcellulose, glucose/sugar syrup, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel or hydrogenated edible fat), emulsifying agents (e.g. lecithin, monooleic acid sorbitol or gum arabic), nonaqueous vehicles (e.g. almond oil, fractionated coconut oil, oily esters, propylene glycol or ethyl alcohol) or any combination of two or more thereof.

When the composition of the invention is formulated in unit dosage form, it preferably contains from 50 to 500 mg of the compound or compounds of the invention per unit dose.

The preparation of the compounds of the present invention is further illustrated by the following Examples and the preparation of certain intermediates is illustrated by the following Preparations. The compounds of the invention are all in the syn configuration.

PREPARATION 1

Pivaloyloxymethyl 3-methoxymethyl-7-phenoxyacetamido-3-cephem-4-carboxylate

1 g of sodium 3-methoxymethyl-7-phenoxyacetamido-3-cephem-4-carboxylate was dissolved in 50 ml of dimethyl sulphoxide, and 975 mg of pivaloyloxymethyl bromide were added thereto, after which the mixture was stirred at room temperature for 15 minutes. The mixture was then diluted with 200 ml of ethyl acetate, washed in turn with 50 ml of a saturated aqueous solution of sodium bicarbonate and 50 ml of a saturated aqueous solution of potassium bisulphate, and then dried over anhydrous magnesium sulphate. After filtering off the drying agent, the filtrate was concentrated under reduced pressure and the resulting residue was chromatographed through 100 g of silica gel eluted with a 1:1 by volume mixture of hexane and ethyl acetate, to afford 750 mg of the desired pivaloyloxymethyl 3-methoxymethyl-7-phenoxyacetamido-3-cephem-4-carboxylate.

Nuclear Magnetic Resonance spectrum ($CDCl_3$) δ ppm: 1.25 (9H, singlet, t-butyl); 3.35 (3H, singlet, OCH_3); 3.54 (2H, singlet, 2-cephem H_2); 4.29 (2H, singlet, CH_2 of methoxymethyl); 4.58 (2H, singlet, (CH_2 of phenoxyacetamido); 5.01 (1H, doublet, $J=5$ Hz, 6-cephem H); 5.6–6.1 (3H, multiplet, 7-cephem H and CH_2 of pivaloyloxymethyl); 6.7–7.6 (6H, multiplet, C_6H_5 and NH).

PREPARATION 2

Pivaloyloxymethyl 7-amino-3-methoxymethyl-3-cephem-4-carboxylate p-toluenesulfonate

488 mg of phosphorus pentachloride were dissolved in 5 ml of dry methylene chloride, and then 120 mg of phosphorus oxychloride were added to the solution. Whilst the mixture was being stirred at room temperature, 247 mg of pyridine were added. The mixture was then cooled to −10° C., and 769 mg of pivaloyloxymethyl 3-methoxymethyl-7-phenoxyacetamido-3-cephem-4-carboxylate were added thereto. The temperature of the mixture was then allowed to rise gradually to room temperature. After stirring the mixture for 2 hours, it was again cooled to 0° C., and then 1.5 ml of propanol were added and the mixture again stirred for 30 minutes. A small amount of water was added to the mixture, which was then stirred for a further 15 minutes. The mixture was diluted with 50 ml of ethyl acetate and washed with a saturated aqueous solution of sodium bicarbonate. The ethyl acetate layer was separated and dried over anhydrous magnesium sulphate. The drying agent was filtered off and the filtrate was concentrated by evaporation under reduced pressure. Diisopropyl ether was added to the residue and the wall of the vessel was scraped. The resulting precipitates were collected by filtration and dried to give 443 mg of the desired pivalo-yloxymethyl 7-amino-3-methoxymethyl-3-cephem-4-carboxylate. This compound was dissolved in 5 ml of ethyl acetate, and then an equimolar amount of p-toluenesulfonic acid monohydrate in 5 ml of ethyl acetate was added to the solution. The resulting mixture was allowed to stand at ambient temperature for 3 hours, affording 523 mg of the title compound melting at 160°–170° C. (with decomposition, recrystallized from methylene chloride and ethyl acetate) in the form of needles.

Elemental Analysis: Calculated for $C_{15}H_{22}N_2O_6S.C_7H_8O_3S$: C, 49.80%; N, 5.70%; N, 5.28%; S, 12.08%. Found: C, 49.76%, H, 5.60%; N, 5.00%; S, 12.06%.

PREPARATION 3

Benzhydryl 7-[2-(2-chloroacetamidothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate

To 0.057 ml of dimethylformamide were added 0.061 ml of phosphorus oxychloride, with ice-cooling and stirring. The mixture was then stirred at 40° C. for 1 hour and then twice subjected to azeotropic distillation with dry methylene chloride. 1 ml of ethyl acetate was added to the resulting mixture, which was then vigorously stirred at room temperature whilst 200 mg of 2-(2-chloroacetamidothiazol-4-yl)-2-methoxyiminoacetic acid were added. Stirring was continued for a further 30 minutes to give a mixture (a).

Meanwhile, 200 mg of benzhydryl 7-amino-3-methoxymethyl-3-cephem-4-carboxylate and 145 mg of N,N-diethylaniline were dissolved in 5 ml of methylene chloride, and the mixture was stirred at −5° C. to give a mixture (b).

Mixture (a) was then added dropwise to mixture (b) and the mixtures were stirred together for 15 minutes, after which the resulting reaction mixture was concentrated by evaporation under reduced pressure. 20 ml of ethyl acetate and 5 ml of water were then added to the residue and the ethyl acetate layer was separated. This layer was washed in turn with 5 ml of a saturated aqueous solution of sodium bicarbonate, 5 ml of a 5% w/v aqueous solution of hydrogen chloride and finally 5 ml of a saturated aqueous solution of sodium chloride, after which the solution was dried over anhydrous magnesium sulphate. The drying agent was filtered off and the filtrate was concentrated by evaporation under reduced pressure. The resulting residue was chromatographed through 30 g of silica gel (Kieselgel 60), eluted with a 3:2 by volume mixture of hexane and ethyl acetate, to give 213 mg of the desired benzhydryl 7-[2-(2-chloroacetamidothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate.

Nuclear Magnetic Resonance spectrum ($CDCl_3$) δ ppm: 3.19 (3H, singlet, OCH_3 of methoxymethyl); 3.51 (2H, singlet, 2-cephem H_2); 4.09 (3H, singlet, OCH_3 of methoxyimino): 4.20 (2H, singlet, CH_2 of methoxymethyl); 4.22 (2H, singlet, CH_2 of chloroacetamido); 5.02 (1H, doublet, $J=5$ Hz, 6-cephem H); 5.86 (1H, doubled doublet, $J=5$ and 9 Hz, 7-cephem H); 6.7–7.6 (12H, multiplet).

PREPARATION 4

7-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylic acid trifluoroacetate

200 mg of benzhydryl 7-[2-(2-chloroacetamidothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate, followed by 45 mg of thiourea, were dissolved in 5 ml of dimethylacetamide. The solution was maintained at room temperature for 2 hours, after which a saturated aqueous solution of sodium bicarbonate was added. The reaction mixture was then extracted with 20 ml of ethyl acetate and the ex-

tract was washed with water to remove excess thiourea and then dried over anhydrous magnesium sulphate. After the drying agent had been filtered off, the filtrate was concentrated by evaporation under reduced pressure. The resulting residue was chromatographed through 30 g of silica gel (Wacogel C-100), eluted with ethyl acetate, to afford 63 mg of benzhydryl 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate.

The whole of this product was dissolved in 2 ml of anisole, and then 1 ml of trifluoroacetic acid was added to the solution, with ice-cooling and stirring. The mixture was then maintained at room temperature for 30 minutes, after which it was concentrated by evaporation under reduced pressure and diisopropyl ether was added to the residue. The resulting precipitates were collected by filtration and dried, to afford 27 mg of 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylic acid trifluoroacetate.

Nuclear Magnetic Resonance spectrum (deuteroacetone/D_2O) δ ppm: 3.29 (3H, singlet, OCH_3 of methoxymethyl); 3.57 (2H, singlet, 2-cephem H_2); 3.96 (3H, singlet, OCH_3 of methoxyimino); 4.27 (2H, singlet, CH_2 of methoxymethyl); 5.15 (1H, doublet, J=5.0 Hz, 6-cephem H); 5.97 (1H, doublet, J=5.0 Hz, 7-cephem H); 6.59 (1H, singlet).

PREPARATION 5

7-[2-(2-Chloroacetamidothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylic acid

A mixture of 7.65 g of benzhydryl 7-[2-(2-chloroacetamidothiazol-4-yl]-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate, 25 ml of methylene chloride, 5 ml of anisole and 20 ml of trichloroacetic acid was allowed to react at room temperature for 30 minutes. At the end of this time, 300 ml of diisopropyl ether were added to the reacton mixture and the resulting precipitates were collected by filtration, giving 5.95 g of 7-[2-(2-chloroacetamidothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylic acid.

Nuclear Magnetic Resonance spectrum (deuteroacetone/deuterodimethyl sulphoxide) δ ppm: 3.30 (3H, singlet, OCH_3 of methoxymethyl); 3.60 (2H, singlet, 2-cephem H_2); 3.97 (3H, singlet, OCH_3 of methoxyimino); 4.25 (2H, singlet, CH_2 of methoxymethyl); 4.37 (2H, singlet, CH_2 of chloroacetamido); 5.20 (1H, doublet, 6-cephem H); 5.90 (1H, doubled doublet, J=5.0 and 9.0 Hz, 7-cephem H); 7.40 (1H, singlet, 5-thiazole H); 9.50 (1H, doublet, J=9 Hz, 7-cephem NH).

PREPARATION 6

7-[2-(2-Aminothiazol-4-yl)-2-ethoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylic acid trifluoroacetate

Following the method of Preparation 3, 225 mg of 2-(2-chloroacetamidothiazol-4-yl)-2-ethoxyiminoacetic acid and 200 mg of benzhydryl 7-amino-3-methoxymethyl-3-cephem-4-carboxylate were reacted to give 280 mg of benzhydryl 7-[2-(2-chloroacetamidothiazol-4-yl)-2-ethoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate, in the form of a yellow powder.

Nuclear Magnetic Resonance spectrum ($CDCl_3$) δ ppm: 1.28 (3H, triplet, $OCH_2\underline{CH_3}$); 3.17 (3H, singlet, OCH_3); 3.50 (2H, broad singlet, 2-cephem H_2); 4.07 (2H. singlet, CH_2 of methoxymethyl); 4.0–4.5 (4H, multiplet, $O\underline{CH_2}CH_3$ and CH_2 of chloroacetamido); 5.07 (1H, doublet, J=5 Hz, 6-cephem H); 5.93 (1H, doubled doublet, J=5 and 9 Hz, 7-cephem H); 6.90 (1H, singlet, 5-thiazole H); 7.06 (1H, singlet, CH of benzhydryl); 7.31 [10H, singlet, $(C_6H_5)_2$]; 8.10 (1H, doublet, J=9 Hz, 7-cephem NH).

191 mg of this benzhydryl 7-[2-(2-chloroacetamidothiazol-4-yl)-2-ethoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate were then treated with 40 mg of thiourea, as described in Preparation 4, to give 117 mg of benzhydryl 7-[2-(2-aminothiazol-4-yl)-2-ethoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate, in the form of a pale pink powder, which was then treated with 1.5 ml of trifluoroacetic acid in a mixture of anisole and methylene chloride. When diisopropyl ether was added to the mixture, a precipitate was obtained and this was collected by filtration, to give 90 mg of 7-[2-(2-aminothiazol-4-yl)-2-ethoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylic acid trifluoroacetate.

Nuclear Magnetic Resonance spectrum (deuterodimethyl sulphoxide) δ ppm: 1.27 (3H, triplet, J=7 Hz, $OCH_2\underline{CH_3}$); 3.23 (3H, singlet, OCH_3); 3.53 (2H, singlet, 2-cephem H_2); 4.16 (2H, quartet, J=7 Hz, $O\underline{CH_2}CH_3$); 4.20 (2H, singlet, CH_2 of methoxymethyl); 5.15 (1H, doublet, J=5 Hz, 6-cephem H); 5.76 (1H, doubled doublet, J=5 and 9 Hz, 7-cephem H); 6.80 (1H, singlet, 5-thiazole H); 9.70 (1H, doublet, J=9 Hz, 7-cephem NH); 8.5–10.0 (4H, broad multiplet, NH_2 and two COOH).

PREPARATION 7

t-Butyl 3-oxo-4-p-toluenesulphonyloxybutyrate

To 50 ml of dry acetonitrile were added 7.1 g of t-butyl 4-bromo-3-oxobutyrate and 9.45 g of silver p-toluenesulphonate, and the mixture was stirred for 3 days at room temperature, whilst shielding it from the light. The reaction mixture was then filtered and the filtrate was concentrated by evaporation in vacuo.

The resulting crystals containing an oily substance were dissolved in ethyl acetate and the insolubles were removed by filtration. The filtrate was concentrated by evaporation in vacuo, to give a brown, oily substance, which was purified by column chromatography through silica gel, eluted with a 4:1 by volume mixture of cyclohexane and ethyl acetate. The resulting colourless, oily substance was recrystallized from a 1:2 by volume mixture of diethyl ether and hexane, to afford 4.5 g of t-butyl 3-oxo-4-p-toluenesulphonyloxybutyrate, in the form of colourless prisms melting at 67°–69° C.

Nuclear Magnetic Resonance spectrum ($CDCl_3$) δ ppm: 1.43 (9H, singlet, t-butyl); 2.43 (3H, singlet, CH_3 of toluene); 3.43 (2H, singlet, —CH_2COO—); 4.60 (2H, singlet, —SO_2OCH_2—); 7.20–7.90 (4H, C_6H_4).

Elemental Analysis: Calculated for $C_{15}H_{20}O_6S$: C, 54.92%, H, 6.15%; S, 9.78%. Found: C, 55.03%; H, 6.07%; S, 9.86%.

PREPARATION 8

t-Butyl 2-hydroxyimino-3-oxo-4-p-toluenesulphonyloxybutyrate

4.5 g of t-butyl 3-oxo-4-p-toluenesulphonyloxybutyrate were dissolved in 40 ml of acetic acid, and then 1.42 g of sodium nitrite were added, at room temperature, to

the solution over a period of 10 minutes. The mixture was then stirred at room temperature for 50 minutes, after which 200 ml of ethyl acetate were added and the mixture was then washed with an aqueous solution of sodium chloride. The ethyl acetate solution was dried over magnesium sulphate and, after filtering off the drying agent, the filtrate was concentrated by evaporation under reduced pressure to give a brown, oily substance. This oily substance was purified by column chromatography through silica gel, eluted with a 4:1 by volume mixture of cyclohexane and ethyl acetate, affording 1.66 g of t-butyl 2-hydroxyimino-3-oxo-4-p-toluenesulphonyloxybutyrate, in the form of colourless crystals, melting at 106°-108° C. (with decomposition, recrystallized from a 1:1 by volume mixture of diethyl ether and petroleum ether).

Nuclear Magnetic Resonance spectrum ($CDCl_3$) δ ppm: 1.52 (9H, singlet, t-butyl); 2.43 (3H, singlet, CH_3 of toluene); 5.04 (2H, singlet, $—SO_2OCH_2CO—$); 7.20–7.92 (4H, C_6H_4); 10.23 (1H, singlet, OH of hydroxyimino).

Elemental Analysis: Calculated for $C_{15}H_{19}NO_7S$: C, 50.48%; H, 5.36%; N, 3.92%, S, 8.98%. Found: C, 50.62%; H, 5.08%; N, 3.83%; S, 8.97%.

PREPARATION 9

t-Butyl 2-methoxyimino-3-oxo-4-p-toluenesulphonyloxybutyrate

To an ice-cooled solution of 1.66 g of t-butyl 2-hydroxyimino-3-oxo-4-p-toluenesulphonyloxybutyrate in 20 ml of dry acetone were added 960 mg of anhydrous potassium carbonate and 0.466 ml of dimethyl sulphate, and then the mixture was stirred at room temperature for 3 hours. The mixture was then poured into ice-water and extracted with methylene chloride. The extract was washed with an aqueous solution of sodium chloride, dried over magnesium sulphate and concentrated by evaporation under reduced pressure to give a brown, oily substance. This was purified by column chromatography through silica gel, eluted with a 4:1 by volume mixture of cyclohexane and ethyl acetate, to afford 650 mg of t-butyl 2-(syn)-methoxyimino-3-oxo-4-p-toluenesulphonyloxybutyrate, as a pale yellow oil.

Nuclear Magnetic Resonance spectrum ($COCl_3$) δ ppm: 1.50 (9H, singlet, t-butyl); 2.43 (3H, singlet, CH_3 of toluene); 4.07 (3H, singlet, OCH_3); 5.05 (2H, singlet, $—SO_2OCH_2CO—$); 7.20–7.90 (4H, C_6H_4).

PREPARATION 10

2-Methoxyimino-3-oxo-4-p-toluenesulphonyloxybutyric acid

To a solution of 478 mg of t-butyl 2-(syn)-methoxyimino-3-oxo-4-p-toluenesulphonyloxybutyrate in 1 ml of methylene chloride were added 2 ml of trifluoroacetic acid, and the mixture was stirred at room temperature for 4 hours. The methylene chloride and the excess trifluoroacetic acid were then distilled off in vacuo, leaving a brown, oily substance, which was dissolved in diisopropyl ether and allowed to stand, affording 178 mg of 2-(syn)-methoxyimino-3-oxo-4-p-toluenesulphonyloxybutyric acid, in the form of colourless crystals melting at 131°-132° C. (with decomposition).

Elemental Analysis: Calculated for $C_{12}H_{13}NO_7S$: C., 45.72%; H, 3.84%; N, 4.45%; S, 10.18%. Found: C, 45.50%; H, 3.92%; N, 4.32%; S, 9.98%.

Nuclear Magnetic Resonance spectrum (deuteroacetone) δppm: 2.47 (3H, singlet, CH_3 of toluene); 4.10 (3H, singlet, OCH_3); 5.20 (2H, singlet $—SO_2OCH_2CO—$); 7.25–7.95 (4H, C_6H_4); 9.80 (1H, broad singlet, COOH).

PREPARATION 11

Pivaloyloxymethyl 7-(2-methoxyimino-3-oxo-4-p-toluenesulphonyloxybutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate

To a suspension of 464 mg of 2-(syn)-methoxyimino-3-oxo-4-p-toluenesulphonyloxybutyric acid in 20 ml of methylene chloride, cooled to −5° C., was added 0.204 ml of triethylamine, and the mixture was stirred for 5 minutes, until completely dissolved. To the resulting solution were added 0.17 ml of oxalyl chloride and a drop of dimethylformamide and the mixture was stirred at −5° C. for 20 minutes. On removing the solvent, there was left 2-(syn)-methoxyimino-3-oxo-4-p-toluenesulphonyloxybutyryl chloride. This was dissolved in 10 ml of methylene chloride, and then 0.394 ml of N,N-diethylaniline, followed by the methylene chloride solution, were added, at −5° C., to a solution of 530 mg of pivaloyloxymethyl 7-amino-3-methoxymethyl-3-cephem-4-carboxylate p-toluenesulphonate in 20 ml of methylene chloride. This mixture was stirred at −5° C. for 5 minutes, after which the solvent was distilled off. The resulting residue was dissolved in ethyl acetate and washed with dilute aqueous hydrochloric acid. The ethyl acetate layer was separated and dried over magnesium sulphate. After filtering off the drying agent, the filtrate was concentrated by evaporation under reduced pressure, to give a brown, oily substance. This was purified by column chromatography through silica gel eluted with a 4:1 by volume mixture of cyclohexane and ethyl acetate, to afford 510 mg of pivaloyloxymethyl 7-[2-(syn)-methoxyimino-3-oxo-4-p-toluenesulphonyloxybutyrylamino]-3-methoxymethyl-3-cephem-4-carboxylate, in the form of a colourless, foamy substance.

Nuclear Magnetic Resonance spectrum ($CDCl_3$) δ ppm: 1.22 (9H, singlet, t-butyl); 2.43 (3H, singlet, CH_3 of toluene); 3.30 (3H, singlet, OCH_3 of methoxymethyl); 3.51 (2H, singlet, 2-cephem H_2); 4.10 (3H, singlet, OCH_3 of methoxyimino); 4.27 (2H, singlet, CH_2 of methoxymethyl); 4.97 (1H, doublet, J=5.0 Hz, 6-cephem H); 5.07 (2H, singlet, $—SO_2OCH_2CO—$); 5.53–5.97 (3H, multiplet, 7-cephem H and $—OCH_2—$ of pivaloyloxymethyl); 7.20–7.93 (5H, multiplet, 7-cephem NH and C_6H_4).

PREPARATION 12

Following the procedure described in Preparation 7, the following compounds were prepared:

t-Butyl 4-methanesulphonyloxy-3-oxobutyrate, as a pale yellow oil.

Nuclear Magnetic Resonance spectrum ($CDCl_3$) δ ppm: 1.47 (9H, singlet, t-butyl); 3.14 (3H, singlet, CH_3SO_2); 3.45 (2H, singlet, $—COCH_2CO—$); 4.87 (2H, singlet, $—SO_2OCH_2CO—$).

t-Butyl 4-ethanesulphonyloxy-3-oxobutyrate, a yellow oil.

Nuclear Magnetic Resonance spectrum ($CDCl_3$) δ ppm: 1.32–1.62 (9H+3H, singlet+triplet, t-butyl+$CH_3CH_2SO_2$); 3.30 (2H, quartet, J=7.0 Hz, $CH_3\underline{CH_2}SO_2$); 3.47 (2H, singlet, $—COCH_2CO—$); 4.87 (2H, singlet, $—SO_2OCH_2CO—$).

t-Butyl 4-benzenesulphonyloxy-3-oxobutyrate, colourless needles melting at 94°–96° C.

Nuclear Magnetic Resonance spectrum ($CDCl_3$) δ ppm: 1.43 (9H, singlet, t-butyl); 3.43 (2H, singlet, $—COCH_2CO—$); 4.63 (2H, singlet, $—SO_2OCH_2CO—$); 7.40–8.03 (5H, multiplet, C_6H_5).

PREPARATION 13

Following the procedure described in Preparation 8, the following compounds were prepared:

t-Butyl 2-hydroxyimino-4-methanesulphonyloxy-3-oxobutyrate, white crystals melting at 103°–104° C. (with decomposition).

Nuclear Magnetic Resonance spectrum ($CDCl_3$/deuteroacetone) δ ppm: 1.57 (9H, singlet, t-butyl); 3.20 (3H, singlet, CH_3 of methanesulphonyl); 5.23 (2H, singlet, $—SO_2OCH_2CO—$); 11.93 (1H, singlet, OH of hydroxyimino).

t-Butyl 4-ethanesulphonyloxy-2-hydroxyimino-3-oxobutyrate, colourless crystals melting at 85°–87° C. (with decomposition).

Nuclear Magnetic Resonance spectrum ($CDCl_3$) δ ppm: 1.47 (3H, triplet, J=7.0 Hz, $\underline{CH_3}CH_2SO_2$); 1.57 (9H, singlet, t-butyl); 3.33 (2H, quartet, J=7.0 Hz, $CH_3\underline{CH_2}SO_2$); 5.23 (2H, singlet, $—SO_2OCH_2CO—$); 10.50 (1H, singlet, OH of hydroxyimino).

t-Butyl 4-benzenesulphonyloxy-2-hydroxyimino-3-oxobutyrate, colourless needles melting at 93°–95° C. (with decomposition).

Nuclear Magnetic Resonance spectrum ($CDCl_3$) δ ppm: 1.57 (9H, singlet, t-butyl); 5.07 (2H, singlet, $—SO_2OCH_2CO—$); 7.40–8.03 (5H, multiplet, C_6H_5); 10.17 (1H, broad singlet, OH of hydroxyimino).

PREPARATION 14

Following the procedures described in Preparation 9, the following compounds were prepared:

t-Butyl 4-methanesulphonyloxy-2-(syn)-methoxyimino-3-oxobutyrate, a colourless oil.

Nuclear Magnetic Resonance spectrum ($CDCl_3$) δ ppm: 1.54 (9H, singlet, t-butyl); 3.19 (3H, singlet, CH_3 of methanesulphonyl); 4.20 (3H, singlet, OCH_3 of methoxyimino); 5.23 (2H, singlet, $—SO_2OCH_2CO—$).

t-Butyl 4-ethanesulphonyloxy-2-(syn)-methoxyimino-3-oxobutyrate, a pale yellow oil.

Nuclear Magnetic Resonance spectrum ($CDCl_3$) δ ppm: 1.43 (3H, triplet, J=7.0 Hz, $\underline{CH_3}CH_2SO_2$); 1.50 (9H, singlet, t-butyl); 3.27 (2H, quartet, J=7.0 Hz, $CH_3\underline{CH_2}SO_2$); 4.07 (3H, singlet, OCH_3 of methoxyimino); 5.18 (2H, singlet, $—SO_2OCH_2CO—$).

t-Butyl 4-benzenesulphonyloxy-2-(syn)-methoxyimino-3-oxobutyrate, a colourless oil.

Nuclear Magnetic Resonance spectrum ($CDCl_3$) δ ppm: 1.50 (9H, singlet, t-butyl); 4.05 (3H, singlet, OCH_3 of methoxyimino); 5.07 (2H, singlet, $—SO_2OCH_2CO—$); 7.30–8.00 (5H, multiplet, C_6H_5).

PREPARATION 15

Following the procedure described in Preparation 10, the following compounds were prepared:

4-Methanesulphonyloxy-2-(syn)-methoxyimino-3-oxobutyric acid, a pale brown oil.

Nuclear Magnetic Resonance spectrum (deuteroacetone) δ ppm: 3.14 (3H, singlet, CH_3 of methanesulphonyl); 4.10 (3H, singlet, OCH_3 of methoxyimino); 5.27 (2H, singlet, $—SO_2OCH_2CO—$); 10.18 (1H, singlet, COOH).

4-Ethanesulphonyloxy-2-(syn)-methoxyimino-3-oxobutyric acid, melting at 85.5°–89° C.

Nuclear Magnetic Resonance spectrum (deuteroacetone) δ ppm: 1.40 (3H, triplet, J=7.0 Hz, $\underline{CH_3}CH_2SO_2$); 3.34 (2H, quartet, J=7.0 Hz, $CH_3\underline{CH_2}SO_2$); 4.13 (3H, singlet, OCH_3 of methoxyimino); 5.33 (2H, singlet, $—SO_2OCH_2CO—$); 11.10 (1H, broad singlet, COOH).

4-Benzenesulphonyloxy-2-(syn)-methoxyimino-3-oxobutyric acid, as crystals.

Nuclear Magnetic Resonance spectrum (deuteroacetone) δ ppm: 4.06 (3H, singlet, OCH_3 of methoxyimino); 5.17 (2H, singlet, $—SO_2OCH_2CO—$); 7.37–8.03 (5H, multiplet, C_6H_5); 10.33 (1H, singlet, COOH).

PREPARATION 16

Following the procedure described in Preparation 11, the following compounds were prepared:

Pivaloyloxymethyl 7-[4-methanesulphonyloxy-2-(syn)-methoxyimino-3-oxobutyrylamino]-3-methoxymethyl-3-cephem-4-carboxylate, a colourless, foamy substance.

Nuclear Magnetic Resonance spectrum ($CDCl_3$) δ ppm: 1.21 (9H, singlet, t-butyl); 3.16 (3H, singlet, CH_3 of methanesulphonyl); 3.30 (3H, singlet, OCH_3 of methoxymethyl); 3.53 (2H, broad singlet, 2-cephem H_2); 4.13 (3H, singlet, OCH_3 of methoxyimino); 4.24 (2H, singlet, CH_2 of methoxymethyl); 4.99 (1H, doublet, J=4.0 Hz, 6-cephem H); 5.23 (2H, singlet, $—SO_2OCH_2CO—$); 5.60–5.93 (3H, multiplet, 7-cephem H and CH_2 of pivaloyloxymethyl); 7.58 (1H, doublet, J=9.0 Hz, 7-cephem NH).

Pivaloyloxymethyl 7-[4-ethanesulphonyloxy-2-(syn)-methoxyimino-3-oxobutyrylamino]-3-methoxymethyl-3-cephem-4-carboxylate, a colourless, foamy substance.

Nuclear Magnetic Resonance spectrum ($CDCl_3$) δ ppm: 1.22 (9H, singlet, t-butyl); 1.43 (3H, triplet, J=7.0 Hz, $\underline{CH_3}CH_2SO_2$); 3.27 (2H, quartet, J=7.0 Hz, $CH_3\underline{CH_2}SO_2$); 3.30 (3H, singlet, OCH_3 of methoxymethyl); 3.54 (2H, broad singlet, 2-cephem H_2); 4.13 (3H, singlet, OCH_3 of methoxyimino); 4.26 (2H, singlet, CH_2 of methoxymethyl); 5.00 (1H, doublet, J=5.0 Hz, 6-cephem H); 5.27 (2H, singlet, $—SO_2OCH_2CO—$); 5.60–5.97 (3H, multiplet, 7-cephem H and CH_2 of pivaloyloxymethyl); 7.55 (1H, doublet, J=9.0 Hz, 7-cephem NH).

Pivaloyloxymethyl 7-[4-benzenesulphonyloxy-2-(syn)-methoxyimino-3-oxobutyrylamino]-3-methoxymethyl-3-cephem-4-carboxylate, a pale yellow, foamy substance.

Nuclear Magnetic Resonance spectrum ($CDCl_3$) δ ppm: 1.22 (9H, singlet, t-butyl); 3.30 (3H, singlet, OCH_3 of methoxymethyl); 3.52 (2H, broad singlet, 2-cephem H_2); 4.10 (3H, singlet, OCH_3 of methoxyimino); 4.27 (2H, singlet, CH_2 of methoxymethyl); 4.98 (1H, doublet, J=5.0 Hz, 6-cephem H); 5.08 (2H, singlet, $—SO_2OCH_2CO—$); 5.60–5.90 (3H, multiplet, 7-cephem H and CH_2 of pivaloyloxymethyl); 7.40–8.03 (6H, multiplet, C_6H_5, and 7-cephem NH).

PREPARATION 17

Pivaloyloxymethyl 7-(4-chloro-3-oxobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate

725 mg of diketene were dissolved in 10 ml of dry methylene chloride and the solution stirred at −20° C. 30 ml of a carbon tetrachloride solution containing 620

mg of chlorine were then added dropwise to the solution, to produce 4-chloro-3-oxobutyryl chloride.

Meanwhile, 2 g of pivaloyloxymethyl 7-amino-3-methoxymethyl-3-cephem-4-carboxylate p-toluenesulphonate and 1.16 ml of N,N-diethylaniline were dissolved in 20 ml of methylene chloride. The resulting solution was cooled to −10° C., and then the 4-chloro-3-oxobutyryl chloride solution obtained as described above was added dropwise thereto. The mixture was then stirred at the same temperature for 30 minutes, after which it was concentrated by evaporation under reduced pressure. The resulting residue was dissolved in 50 ml of ethyl acetate and then washed in turn with water, a 5% w/v aqueous solution of hydrogen chloride and an aqueous solution of sodium chloride, after which it was dried over anhydrous magnesium sulphate and concentrated by evaporation under reduced pressure. The residue was dissolved in 3 ml of methylene chloride, and 30 ml of diethyl ether were added thereto, after which the mixture was allowed to stand. The resulting needle-like crystals were collected by filtration, washed with diethyl ether and dried to give 1.47 g of the title compound, melting at 131.5°–132.5° C.

Nuclear Magnetic Resonance spectrum ($CDCl_3$) δ ppm: 1.23 (9H, singlet, t-butyl); 3.31 (3H, singlet, OCH_3); 3.54 (2H, singlet, 2-cephem H_2); 3.65 (2H, singlet, CH_2); 4.26 (2H, singlet, CH_2); 4.29 (2H, singlet, CH_2); 4.97 (1H, doublet, $J=5.5$ Hz, 6-cephem H); 5.65–6.0 (3H, multiplet, 7-cephem H and CH_2 of pivaloyloxymethyl); 7.64 (1H, doublet, $J=9$ Hz, 7-cephem NH).

PREPARATION 18

Pivaloyloxymethyl 7-(4-chloro-2-hydroxyimino-3-oxobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate

2.57 g of pivaloyloxymethyl 7-(4-chloro-3-oxobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate were dissolved in 25 ml of acetic acid, and then 409 mg of sodium nitrite were added, little by little, at room temperature to the solution, after which the mixture was stirred for 30 minutes. The mixture was then diluted with 200 ml of ethyl acetate, washed three times with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulphate and then concentrated by evaporation under reduced pressure. The residue was twice subjected to azeotropic distillation using toluene and the resulting residue was dried, giving 2.7 g of the title compound as a foamy solid.

Nuclear Magnetic Resonance spectrum ($CDCl_3$) δ ppm: 1.23 (9H, singlet, t-butyl); 3.33 (3H, singlet, OCH_3 of methoxymethyl); 3.59 (2H, singlet, 2-cephem H_2); 4.33 (2H, singlet, CH_2 of methoxymethyl); 4.75 (2H, singlet, $ClCH_2$); 5.05 (1H, doublet, $J=5.5$ Hz, 6-cephem H); 5.6–6.1 (3H, multiplet, 7-cephem H and CH_2 of pivaloyloxymethyl); 9.3 (1H, doublet, $J=9$ Hz, 7-cephem NH).

PREPARATION 19

Pivaloyloxymethyl 7-[4-chloro-2-(syn)-methoxyimino-3-oxobutyrylamino]-3-methoxymethyl-3-cephem-4-carboxylate

5g of pivaloyloxymethyl 7-(4-chloro-2-hydroxyimino-3-oxobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate were dissolved in 40 ml of tetrahydrofuran. To the resulting solution was added a solution of 2 g of sodium carbonate in 40 ml of water, followed by 5 g of dimethyl sulphate, after which the mixture was stirred for 30 minutes. The mixture was then diluted with 150 ml of ethyl acetate, and washed twice with each in turn of a saturated aqueous solution of sodium biacarbonate and a saturated aqueous solution of potassium bisulphate, after which it was dried over anhydrous magnesium sulphate and concentrated by evaporation under reduced pressure. The residue was chromatographed through 100 g of silica gel eluted with a 3:1 by volume mixture of chloroform and ethyl acetate, to give a solid containing the title compound. This solid was dissolved in 30 ml of diethyl ether and then left to stand under ice-cooling, to produce crystals, which were washed with diethyl ether and then dried, affording 1.9 g of the title compound as needles melting at 168.5°–169.5° C.

Nuclear Magnetic Resonance spectrum ($CDCl_3$) δ ppm: 1.24 (9H, singlet, t-butyl); 3.33 (3H, singlet, OCH_3 of methoxymethyl); 3.57 (2H, singlet, 2-cephem H_2); 4.19 (3H, singlet, OCH_3 of methoxyimino); 4.30 (2H, singlet, CH_2 of methoxymethyl); 4.60 (2H, singlet, $ClCH_2$); 5.03 (1H, doublet, $J=5.5$ Hz, 6-cephem H); 5.6–6.1 (3H, multiplet, 7-cephem H and CH_2 of pivaloyloxymethyl); 7.19 (1H, doublet, $J=9$ Hz NH).

PREPARATION 20

Pivaloyloxymethyl 7-[4-chloro-2-(syn)-ethoxyimino-3-oxobutyrylamino]-3-methoxymethyl-3-cephem-4-carboxylate

The procedure described in Preparation 19 was repeated, but using diethyl sulphate in place of the dimethyl sulphate. The title compound was obtained in the form of needles melting at 171°–172° C.

Nuclear Magnetic Resonance spectrum ($CDCl_3$) δ ppm: 1.23 (9H, singlet, t-butyl); 1.39 (3H, triplet, $J=7$ Hz); 3.35 (3H, singlet, OCH_3); 3.57 (2H, singlet, 2-cephem H_2); 4.32 (2H, singlet, CH_2 of methoxymethyl); 4.43 (2H, quartet, $J=7$ Hz); 4.60 (2H, singlet, $ClCH_2$); 5.04 (1H, doublet, $J=5.5$ Hz, 6-cephem H); 5.6–6.1 [3H, multiplet, 7-cephem H and CH_2 of pivaloyloxy-methyl] 7.17 (1H, doublet, $J=9$ Hz, 7-cephem NH).

PREPARATION 21

Pivaloyloxymethyl 7-[2-(2-formamidothiazol-4-yl)glyoxylamido]-3-methoxymethyl-3-cephem-4-carboxylate

To 0.544 ml of N,N-dimethylformamide was added, with ice-cooling, 0.582 ml of phosphorus oxychloride, and the resulting mixture was stirred at 40°–45° C. for 1 hour. The low boiling point materials were removed by allowing the mixture to stand for 5 minutes in vacuo, after which 10 ml of ethyl acetate, 1.25 g of 2-(2-formamidothiazol-4-yl)glyoxylic acid and 3 ml of N,N-dimethylformamide were added, in turn, to the resulting residue at room temperature. The mixture was stirred for 40 minutes and then added to a solution of 2.9 g of pivaloyloxymethyl 7-amino-3-methoxymethyl-3-cephem-4-carboxylate p-toluenesulphonate and 2.9 ml of N,N-diethylaniline in 30 ml of methylene chloride at a temperature of −20° C. to −30° C. The mixture was then stirred at 0° C. for 30 minutes, after which it was diluted with chloroform, washed in turn, with an aqueous solution of potassium bisulphite and an aqueous solution of sodium bicarbonate, and then dried over anhydrous magnesium sulphate. The solvent was removed by distillation and the residue was purified by column chromatography through silica gel eluted with

2:1 by volume mixture of ethyl acetate and chloroform, to give 1.9 g of the title compound in the form of an amorphous powder.

Nuclear Magnetic Resonance sepctrum (deuterodimethylsulphoxide) δ ppm: 1.22 (9H, singlet, t-butyl); 3.32 (3H, singlet, OCH_3); 3.57 (2H, broad singlet, 2-cephem H_2) 4.32 (2H, broad singlet, CH_2 of methoxymethyl); 5.07 (1H, singlet, 6-cephem H); 5.7–6.0 (3H, multiplet, —$COOCH_2O$— and 7-cephem H); 8.03 (1H, broad doublet, J=9 Hz, 7-cephem NH); 8.97 (1H, singlet); 9.05 (1H, broad singlet).

PREPARATION 22

1-Ethoxycarbonyloxyethyl 7-[2-(2-formamidothiazol-4-yl)glyoxylamido]-3-methoxymethyl-3-cephem-4-carboxylate

The procedure described in Preparation 21 was repeated, but using 2.8 g of 1-ethoxycarbonyloxyethyl 7-amino-3-methoxymethyl-3-cephem-4-carboxylate p-toluenesulphonate and 1.25 g of 2-(2-formamidothiazol-4-yl)glyoxylic acid, to give 1.5 g of the title compound.

Nuclear Magnetic Resonance spectrum ($CDCl_3$) δ ppm: 1.31 (3H, triplet, J=7 Hz, OCH_2CH_3); 1.59 (3H, doublet, J=6 Hz, CH_3 of carbonyloxyethyl); 3.32 (3H, singlet, OCH_3 of methoxymethyl); 3.56 (2H, broad singlet, 2-cephem H); 4.22 (1H, quartet; J=7 Hz, OCH_2CH_3) 4.32 (2H, singlet, CH_2 of methoxymethyl); 5.03 (1H, doublet, J=5 Hz, 6-cephem H); 6.00 (1H, doubled doublet, J=5+9 Hz, 7-cephem H); 6.7–7.1 (1H, multiplet, $CHCH_3$); 7.38 (1H, singlet, 5-thiazole H); 8.01 (1H, doublet, J=9 Hz, 7-cephem H); 8.60 (1H, singlet, HCO); 9–12 (broad singlet (HCONH).

EXAMPLE 1

Pivaloyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate

To 71 mg of dimethylformamide were added, with ice-cooling and stirring, 135 mg of phosphorus oxychloride. The mixture was stirred at 40° C. for 1 hour and then subjected twice to azeotropic distillation using dry methylene chloride. To the resulting mixture was added 1 ml of ethyl acetate, after which, 265 mg of 2-(2-chloroacetamidothiazol-4-yl]-2-methoxyiminoacetic acid were added, with vigorous stirring at room temperature, to the mixture and stirring was continued for 30 minutes.

Meanwhile, 121 mg of pivaloyloxymethyl 7-amino-3-methoxymethyl-3-cephem-4-carboxylate and 141 mg of N,N-diethylaniline were dissolved in 5 ml of methylene chloride and stirred at −5° C. The resulting mixture was added dropwise to the mixture containing 2-(2-chloroacetamidothiazol-4-yl)-2-methoxyiminoacetic acid prepared as described above. The reaction mixture was stirred for 15 minutes and then concentrated by evaporation under reduced pressure. To the residue were added 20 ml of ethyl acetate and 5 ml of water, and the ethyl acetate layer was separated, washed, in turn, with 5 ml of a saturated aqueous solution of sodium bicarbonate, 5 ml of a 5% w/v aqueous solution of hydrogen chloride and 5 ml of a saturated aqueous solution of sodium chloride, and finally dried over anhydrous magnesium sulphate. The drying agent was filtered off and the filtrate was concentrated by evaporation under reduced pressure. The resulting residue was subjected to column chromatography through 10 g of silica gel eluted with a 2:1 by volume mixture of ethyl acetate and hexane, to afford 55 mg of pivaloyloxymethyl 7-[2-(2-chloroacetamidothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate.

This product was dissolved in 1 ml of dimethylacetamide, and 13.5 mg of thiourea were added to the resulting solution, which was then stirred at room temperature for 2 hours. The reaction mixture was then diluted with 20 ml of ethyl acetate, washed with a saturated aqueous solution of sodium bicarbonate and dried over anhydrous magnesium sulphate. The drying agent was filtered off and the filtrate was concentrated by evaporation under reduced pressure. The residue was subjected to column chromatography through 5 g of silica gel eluted with a 3:1 by volume mixture of ethyl acetate and hexane, to afford 36 mg of the title compound.

Nuclear Magnetic Resonance spectrum (deutroacetone) δ ppm: 1.19 (9H, singlet, t-butyl); 3.23 (3H, singlet, OCH_3 of methoxymethyl); 3.52 (2H, singlet, 2-cephem H_2); 3.90 (3H, singlet, OCH_3 of methoxyimino); 4.18 (2H, singlet, CH_2 of methoxymethyl); 5.12 (1H, doublet, J=5 Hz, 6-cephem H); 5.8–6.1 (3H, multiplet, 7-cephem H and CH_2 of pivaloyloxymethyl); 6.78 (1H, singlet, 5-thiazole H); 6.6–7.1 (2H, broad singlet, NH_2); 8.01 (1H, doublet, J=9 Hz, 7-cephem NH).

EXAMPLE 2

Following the procedure described in Example 1, the following compounds were prepared:

Acetoxymethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate.

Nuclear Magnetic Resonance spectrum (deuteroacetone) δ ppm: 2.10 (3H, singlet, CH_3CO); 3.22 (3H, singlet, OCH_3 of methoxymethyl); 3.52 (2H, singlet, 2-cephem H_2); 3.92 (3H, singlet, OCH_3 of methoxyimino); 4.20 (2H, singlet, CH_2 of methoxymethyl); 5.11 (1H, doublet, J=5 Hz, 6-cephem H); 5.6–6.3 (3H, multiplet, CH_2 of acetoxymethyl and 7-cephem H); 6.76 (1H, singlet, 5-thiazole H); 6.6–7.1 (2H, broad singlet, NH_2); 8.03 (1H, doublet, J=9 Hz, 7-cephem NH).

Isovaleryloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate

Nuclear Magnetic Resonance spectrum ($CDCl_3$) δ ppm: 0.99 (6H, doublet, J=6.5 Hz, two CH_3 of isovaleryl); 1.3–2.1 (1H, multiplet, CH of isovaleryl); 2.2–2.5 (2H, multiplet, CH_2 of isovaleryl); 3.32 (3H, singlet, OCH_3 of methoxymethyl); 3.56 (2H, broad singlet, 2-cephem H_2); 3.98 (3H, singlet, OCH_3 of methoxyimino); 4.30 (2H, singlet, CH_2 of methoxymethyl); 5.06 (1H, doublet, J=5.0 Hz,6-cephem H); 5.8 (2H, broad singlet, NH_2); 5.92 (2H, singlet, $COOCH_2OCO$); 6.08 (1H, doubled doublet, J=5.0 and 9.0 Hz, 7-cephem H); 6.70 (1H, singlet, 5-thiazole H); 8.20 (1H, doublet, J=9.0 Hz, 7-cephem NH).

Pivaloyloxymethyl 7-[2-(2-aminothiazole-4-yl)-2-ethoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate, having the properties described in Example 8.

EXAMPLE 3

Following the prcedure described in Example 1, 1-ethoxycarbonyloxyethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate was prepared.

Nuclear Magnetic Resonance spectrum ($CDCl_3$) δ ppm: 1.32 1.30 (3H, triplet, OCH_2CH_3); 1.59 1.61 (3H,

doublet, CH_3 of carbonyloxyethyl); 3.33 3.32 (3H, singlet, OCH_3 of methoxymethyl); 3.57 (2H, singlet, 2-cephem H_2); 4.03 (3H, singlet, OCH_3 of methoxyimino); 4.23 4.21 (2H, quartet, OCH_2CH_3); 4.34 4.30 (2H, singlet, CH_2 of methoxymethyl); 5.05 5.10 (1H, doublet, J=5 Hz, 6-cephem H); 5.59 [1H, doubled doublet J=5+9 Hz, 7-cephem H]; 5.73 [2H, broad singlet NH_2]; 6.73 6.70 [1H, singlet, 5-thiazole H]; 6.7–7.1 [1H, multiplet, CH of ethoxycarbonyloxyethyl]; 7.90 [1H, doublet, J=9 Hz, 7-cephem NH].

EXAMPLE 4

Pivaloyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate

To 10 ml of dimethyl sulphoxide were added 1 g of 7-[2-(2-chloroacetamidothiazol-4-yl)-2-(syn)-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylic acid, 380 mg of bromomethyl pivalate and 240 mg of potassium fluoride, after which the mixture was stirred at room temperature for 1 hour. The mixture was then diluted with 100 ml of ethyl acetate and washed successively with water, a 5% w/v aqueous solution of sodium bicarbonate, a 10% w/v aqueous solution of potassium bisulphate and a saturated aqueous solution of sodium chloride, after which it was dried over anhydrous magnesium sulphate. The solvent was then distilled off under reduced pressure and the resulting residue was subjected to column chromatography through silica gel eluted with a 1:1 by volume mixture of chloroform and ethyl acetate, to give 300 mg of pivaloyloxymethyl 7-[2-(2-chloroacetamidothiazol-4-yl)-2-(syn)-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate as a pale yellow powder.

This compound was dissolved, with 60 mg of thiourea, in 3 ml of dimethylacetamide, and the solution was stirred at room temperature for 4 hours. The mixture was then poured into 10 ml of a saturated aqueous solution of sodium bicarbonate and extracted with ethyl acetate. The extract was washed with, in turn, a 10% w/v aqueous solution of potassium bisulphate and a saturated aqueous solution of sodium chloride, after which it was dried over magnesium sulphate and concentrated by evaporation under reduced pressure. The residue was purified by column chromatography through silica gel eluted with a 3:1 by volume mixture of ethyl acetate and hexane to give 200 mg of the title compound. This compound was identified by nuclear magnetic resonance and found to be identical with the compound obtained in Example 1.

EXAMPLE 5

Isobutyryloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate

The procedure described in Example 4 was repeated, except that the bromomethyl pivalate was replaced by 360 mg of bromomethyl isobutyrate. There were obtained 180 mg of isobutyryloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-(syn)-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate, as a slightly yellow powder.

Nuclear Magnetic Resonance spectrum ($CDCl_3$) δ ppm: 1.20 (6H, doublet, J=6.5 Hz, two CH_3 of isobutyryl); 2.66 (1H, septet, J=6.5 Hz, CH of isobutyryl); 3.21 (3H, singlet, OCH_3 of methoxymethyl); 3.40 (2H, AB quartet, 2-cephem H_2); 4.01 (3H, singlet, OCH_3 of methoxyimino); 4.16 (2H, singlet, CH_2 of methoxymethyl); 5.05 (1H, doublet, J=5 Hz, 6-cephem H); 5.6–6.2 (5H, multiplet, NH_2, CH_2 of carbonyloxymethyl and 7-cephem H); 6.65 (1H, singlet, 5-thiazole H); 8.06 (1H, doublet, J=9 Hz, 7-cephem NH).

EXAMPLE 6

Propionyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate

The procedure described in Example 4 was repeated except that the bromomethyl pivalate was replaced by 340 mg of bromomethyl propionate, to give 165 mg of the title compound as an almost colourless powder.

Nuclear Magnetic Resonance spectrum ($CDCl_3$) δ ppm: 1.17 (3H, triplet, J=6.5 Hz, CH_2CH_3); 2.41 (2H, quartet, J=6.5 Hz, CH_2CH_3); 3.20 (3H, singlet, CH_3 of methoxymethyl); 3.35 (2H, AB quartet, 2-cephem H_2); 4.02 (3H, singlet, OCH_3 of methoxyimino); 4.17 (2H, singlet, CH_2 of methoxymethyl); 5.09 (1H, doublet, J=5 Hz, 6-cephem H); 5.6–6.3 (5H, multiplet, NH_2, CH_2 of carbonyloxymethyl and 7-cephem H); 6.68 (1H, singlet, 5-thiazole H); 8.25 (1H, doublet, J=9 Hz, 7-cephem NH).

EXAMPLE 7

Pivaloyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate

To a solution of 45 mg of sodium 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate (prepared from the corresponding trifluoroacetate) in 1 ml of dimethylacetamide were added, at −15° C., 27 mg of iodomethyl pivalate and the mixture was allowed to react for 15 minutes. At the end of this time, 20 ml of ethyl acetate were added to the reaction mixture, and the mixture was washed, in turn, with water, an aqueous solution of potassium bisulphate and an aqueous solution of sodium bicarbonate. The organic phase was separated and concentrated by evaporation under reduced pressure, and the residue was subjected to column chromatography through silica gel eluted with a 3:1 by volume mixture of ethyl acetate and hexane, to give 49 mg of the title compound, whose properties were identical with those of the compound obtained in Example 1.

EXAMPLE 8

Pivaloyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-ethoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate

The procedure described in Example 7 was repeated, except that sodium 7-[2-(2-aminothiazol-4-yl)-2-ethoxyiminoacetamido]—3-methoxymethyl-3-cephem-4-carboxylate and iodomethyl pivalate were used, to give the title compound.

Nuclear Magnetic Resonance spectrum ($CDCl_3$) δ ppm: 1.22 (9H, singlet, t-butyl); 1.31 (3H, triplet, OCH_2CH_3); 3.30 (3H, singlet, OCH_3 of methoxymethyl); 3.53 (2H, singlet, 2-cephem H_2); 4.28 (2H, quartet, OCH_2CH_3); 4.30 (2H, singlet, CH_2 of methoxymethyl); 5.01 (1H, doublet, J=5 Hz, 6-cephem H); 5.7–6.2 (5H, multiplet, 7-cephem H, NH_2 and CH_2 of carbonyloxymethyl); 6.76 (1H, singlet, 5-thiazole H); 7.70 (1H, doublet, 5=9 Hz, 7-cephem NH).

EXAMPLE 9

1-Ethoxycarbonyloxyethyl 7-[2-(2-aminothiazol-4-yl)-2-ethoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate

To a solution of 500 mg of sodium 7-[2-(2-aminothiazol-4-yl)-2-ethoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate in 5 ml of N,N-dimethylacetamide were added, with ice-cooling, 395 mg of 1-iodoethyl ethylcarbonate, and then the mixture was stirred at room temperature for 30 minutes. At the end of this time, 50 ml of ethyl acetate were added to the reaction mixture, which was then washed with, in turn, 20 ml of water, 20 ml of a saturated aqueous solution of sodium bicarbonate and 20 ml of an aqueous solution of sodium chloride. The mixture was then dried over anhydrous magnesium sulphate and the solvent was removed by distillation under reduced pressure, giving a residue, which was chromatographed through 20 g of silica gel eluted with ethyl acetate, to afford 460 mg of the title compound.

Nuclear Magnetic Resonance spectrum ($CDCl_3$) δ ppm: 1.30 (3H, triplet, $\underline{CH_3}CH_2$); 1.32 (3H, triplet, $\underline{CH_3}CH_2$); 1.59 (3H, doublet, $J=6.0$ Hz, CH_3 of carbonyloxyethyl); 3.30 (3H, singlet, OCH_3 of methoxymethyl); 3.52 (2H, broad singlet, 2-cephem H_2); 4.22 (2H, quartet, CH_3e,uns/CH_2); 4.27 (2H, quartet, $CH_3\underline{CH_2}$); 4.30 (2H, singlet, CH_2 of methoxymethyl); 5.05 (1H, doublet, $J=5.0$ Hz, 6-cephem H); 5.8 (2H, broad singlet, NH_2); 6.00 (1H, doubled doublet, J 5.0+9.0 Hz, 7-cephem H); 6.75 (1H, singlet, 5-thiazole H); 6.7–7.1 (1H, multiplet, CH carbonyloxyethyl); 7.8 (1H, doublet, $J=9$ Hz, 7-cephem NH).

EXAMPLE 10

Pivaloyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate

To a solution of 510 mg of pivaloyloxymethyl 7-[2-(syn)-methoxyimino-3-oxo-4-p-toluenesulphonyloxybutyrylamino]-3-methoxymethyl-3-cephem-4-carboxylate in 5 ml of ethanol were added 76 mg of thiourea and 84 mg of sodium acetate. 3 ml of water were then added dropwise to the mixture, after which the whole mixture was stirred at room temperature for 3.5 hours. At the end of this time, the ethanol was removed by distillation and the residue was dissolved in ethyl acetate, washed with an aqueous solution of sodium chloride and dried over anhydrous magnesium sulphate. The ethyl acetate was distilled off, giving a pale brown, foamy substance, which was purified by column chromatography through silica gel eluted with a 2:1 by volume mixture of ethyl acetate and methylene chloride, affording 392 mg of the title compound, in the form of a colourless foamy substance having the same properties as the product of Example 1.

EXAMPLE 11

Propionyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate

The procedure described in Example 10 was repeated, but using 490 mg of propionyloxymethyl 7-[2-(syn)-methoxyimino-3-oxo-4-p-toluenesulphonyloxybutyrylamino]-3-methoxymethyl-3-cephem-4-carboxylate, to give 370 mg of the title compound, having properties identical with those of the product of Example 6.

EXAMPLE 12

The procedure described in Example 10 was repeated, except that the pivaloyloxymethyl 7-[2-(2-(syn)-methoxyimino-3-oxo-4-p-toluenesulphonyloxybutyrylamino]-3-methoxymethyl-3-cephem-4-carboxylate was replaced by 1-ethoxycarbonyloxyethyl 7-[2-(syn)-methoxyimino-3-oxo-4-p-toluenesulphonyloxybutyrylamino]-3-methoxymethyl-3-cephem-4-carboxylate or isobutyryloxymethyl 7-[2-(syn)-methoxyimino-3-oxo-4-p-toluenesulphonyloxybutyrylamino]-3-methoxymethyl-3-cephem-4-carboxylate, to give 1-ethoxycarbonyloxyethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate (having properties idential with those of the product of Example 3) and isobutyryloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate (having properties identical with those of the product of Example 5), respectively.

EXAMPLE 13

The procedure described in Example 10 was repeated, except that 465 mg of pivaloyloxymethyl 7-[4-methanesulphonyloxy-2-(syn)-methoxyimino-3-oxobutyrylaminol-3-methoxymethyl-3-cephem-4-carboxylate and 152 ...g of thiourea were used, to give 390 mg of pivaloyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate, having properties identical with those of the product of Example 1.

The same compound was also obtained following the same procedure, but using, in separate experiments, pivaloyloxymethyl 7-[4-ethanesulphonyloxy-2-(syn)-methoxyimino-3-oxobutyrylamino]-3-methoxymethyl-3-cephem-4-carboxylate or pivaloyloxymethyl 7-[4-benzenesulphonyloxy-2-(syn)-methoxyimino-3-oxobutyrylamino]-3-methoxymethyl-3-cephem-4-carboxylate.

EXAMPLE 14

Pivaloyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate

47 mg of pivaloyloxymethyl 7-[4-chloro-2-(syn)-methoxyimino-3-oxobutyrylamino]-3-methoxymethyl-3-cephem-4-carboxylate were dissolved in 5 ml of dimethylacetamide and then 14 mg of thiourea were added to the solution, which was then stirred at room temperature for 4 hours. The reaction mixture was diluted with 50 ml of ethyl acetate, washed three times, each time with 15 ml of water, dried over anhydrous magnesium sulphate and then concentrated by evaporation under reduced pressure. The resulting residue was dissolved in 1 ml of chloroform, and 20 ml of diisopropyl ether were added to the resulting solution. The precipitate produced was collected by filtration and dried, to give 50 mg of the title compound as a colourless powder having properties identical with those of the product of Example 1.

EXAMPLE 15

Pivaloyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-ethoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate

The procedure described in Example 14 was repeated, except that the pivaloyloxymethyl 7-[4-chloro-2-(syn)-methoxyimino-3-oxobutyrylamino]-3-methoxymethyl-3-cephem-4-carboxylate was replaced by pivaloyloxymethyl 7-[4-chloro-2-(syn)-ethoxyimino-3-oxobutyrylamino]-3-methoxymethyl-3-cephem-4-carboxylate, to give the title compound as a colourless powder having properties identical with those of the product of Example 8.

EXAMPLE 16

Pivaloyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate

(a) A solution of 0.25 g of pivaloyloxymethyl 7-[2-(2-formamidothiazol-4-yl)glyoxylamido]-3-methoxymethyl-3-cephem-4-carboxylate and 65 mg of methoxyamine hydrochloride in 2 ml of dimethylacetamide was stirred at 40° C. for 140 minutes. At the end of this time, ethyl acetate was added to the reaction mixture, which was then washed with a saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulphate. The solvent was removed by distillation and the residue was subjected to column chromatography through silica gel, eluted with a 2:1 by volume mixture of ethyl acetate and chloroform, to give 0.2 g of crude pivaloyloxymethyl 7-[2-(2-formamidothiazol-4-yl)-2-(syn)-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate, which was further purified by recrystallization from 1 ml of ethyl acetate, to give 170 mg of crystals melting at 172° C. (with decomposition).

Nuclear Magnetic Resonance spectrum (deuterodimethyl sulphoxide) δ ppm: 1.18 (9H, singlet, t-butyl); 3.22 (3H, singlet, OCH_3 of methoxymethyl); 3.58 (2H, broad singlet, 2-cephem H_2); 3.88 (3H, singlet, OCH_3 of methoxyimino); 4.14 (2H, singlet, CH_2 of methoxymethyl); 5.19 (1H, doublet, J=5 Hz, 6-cephem H); 5.82 (3H, multiplet, CH_2 of pivaloyloxymethyl and 7-cephem H); 7.37 (1H, singlet, 5-thiazole H); 8.47 (1H, singlet, HCO); 9.66 (1H, doublet, J=9 Hz, 7-cephem NH); 12.58 (1H, broad singlet, NH of formamido).

(b) To a solution of 2.6 g of the pivaloyloxymethyl 7-[2-(2-formamidothiazol-4-yl)-2-(syn)-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate prepared as described above in 72 ml of methanol were added, with ice-cooling, 0.7 ml of concentrated hydrochloric acid, and the mixture was stirred at room temperature for 2.5 hours. The methanol was removed by distillation in vacuo, and then 20 ml each of ethyl acetate and water were added to the residue, after which the mixture was neutralized by the addition of a saturated aqueous solution of sodium bicarbonate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried and then concentrated by evaporation under reduced pressure. The residue was dissolved in 13 ml of chloroform and the solution was added dropwise, with stirring, to 100 ml of diisopropyl ether. The resulting precipitate was collected by filtration, to give 2.2 g of the title compound in the form of a colourless powder whose properties were identical with those of the product of Example 1.

EXAMPLE 17

Pivaloyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-ethoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate

The procedure described in Example 16(a) was repeated, except that the methoxyamine hydrochloride was replaced by 75 mg of ethoxyamine hydrochloride, to give 150 mg of pivaloyloxymethyl 7-[2-(syn)-ethoxyimino-2-(2-formamidothiazol-4-yl)acetamido]-3-methoxymethyl-3-cephem-4-carboxylate, in the form of crystals melting at 153° C.

Nuclear Magnetic Resonance spectrum (deuterodimethyl (sulphoxide) δ ppm: 1.18 (9H, singlet, t-butyl); 1.28 (3H, triplet, $OCH_2\underline{CH_3}$); 3.21 (3H, singlet, OCH_3 of methoxymethyl); 3.58 (2H, broad singlet, 2-cephem H_2); 4.15 (2H, singlet, CH_2 of methoxymethyl); 4.19 (2H, quartet, $O\underline{CH_2}CH_3$); 5.19 (1H, doublet, J=5 Hz, 6-cephem H); 5.71-5.95 (3H, multiplet, CH_2 of pivaloyloxymethyl and 7-cephem H); 7.38 (1H, singlet, 5-thiazole H); 8.48 (1H, singlet, HCO); 9.64 (1H, doublet, J=8 Hz, 7-cephem NH); 12.60 (1H, broad singlet, NH of formamido).

The procedure described in Example 16(b) was repeated, except that 9.65 g of pivaloyloxymethyl 7-[2-(syn)-ethoxyimino-2-(2-formamidothiazol-4-yl)acetamido]-3-methoxymethyl-3-cephem-4-carboxylate, 170 ml of methanol and 2 ml of concentrated hydrochloric acid were reacted at room temperature for 3 hours, to give 8.7 g of the title compound in the form of a colourless powder whose properties were identical to those of the product of Example 8.

EXAMPLE 18

1-Ethoxycarbonyloxyethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate

A mixture of 180 mg of 1-ethoxycarbonyloxyethyl 7-[2-(2-formamidothiazol-4-yl)-2-(syn)-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate, 5 ml of methanol and 0.05 ml of concentrated hydrochloric acid were reacted as described in Example 16(b), to give 120 mg of the title compound, in the form of a pale yellow powder whose properties were identical with those of the product of Example 3.

EXAMPLE 19

Methoxycarbonyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate

To a solution of 500 mg of sodium 7-[2-(2-aminothiazol-4-yl)-2-(syn)-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate in 5 ml of dimethylacetamide were added, with ice-cooling, 500 mg of iodomethyl methylcarbonate, and the mixture was stirred for 30 minutes. At the end of this time, the reaction mixture was diluted with 50 ml of ethyl acetate, washed, in turn, with a saturated aqueous solution of sodium bicarbonate and an aqueous solution of sodium chloride and dried over anhydrous magnesium sulphate. The magnesium sulphate was removed by filtration and the filtrate was concentrated by evaporation under reduced pressure. The residue was purified by column chromatography through silica gel, eluted with ethyl acetate, to give 433 mg of the title compound in the form of a foamy substance.

Nuclear Magnetic Resonance spectrum ($CDCl_3$) δ ppm: 3.31 (3H, singlet, OCH_3 of methoxymethyl); 3.56 (2H, broad singlet, 2-cephem H_2); 3.84 (3H, singlet, OCH_3 of methoxycarbonyl); 4.00 (3H, singlet, OCH_3 of methoxyimino); 4.31 (2H, singlet, CH_2 of methoxymethyl); 5.05 (1H, doublet, 6-cephem H); 5.5–6.3 (5H, multiplet, 7-cephem H, CH_2 of carbonyloxymethyl and NH_2); 6.68 (1H, singlet, 5-thiazole H); 8.10 (1H, doublet, J = 9.0 Hz, 7-cephem NH).

EXAMPLE 20

Ethoxycarbonyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate

To a solution of 861 mg of sodium 7-[2-(2-chloroacetamidothiazol-4-yl]-2-(syn)-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate in 8.6 ml of dimethylacetamide were added, at −10° C., 565 mg of iodomethyl ethylcarbonate and the mixture was stirred for 1 hour. At the end of this time, 100 ml of ethyl acetate were added to the reaction mixture, which was then washed, in turn, with water, a saturated aqueous solution of sodium bicarbonate and an aqueous solution of sodium chloride, and then dried over magnesium sulphate. The organic layer was concentrated by evaporation under reduced pressure and the residue was purified by column chromatography through silica gel eluted with a 2:1 by volume mixture of ethyl acetate and chloroform. to give 696 mg of ethoxycarbonyloxymethyl 7-[2-(2-chloroacetamidothiazol-4-yl)-2-(syn)-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate.

The whole of this compound was dissolved in 6.4 ml of dimethylacetamide, and 800 mg of thiourea were added to the resulting solution, after which the mixture was stirred at room temperature overnight. The mixture was then diluted with 100 ml of ethyl acetate, washed three times with water and dried over anhydrous magnesium sulphate. The solvent was removed by distillation and the residue was subjected to column chromatography through silica gel eluted with ethyl acetate, to give 220 mg of the title compound in the form of a foamy substance.

Nuclear Magnetic Resonance spectrum ($CDCl_3$) δ ppm: 1.32 (3H, triplet, J = 7 Hz, CH_3 of ethoxy); 3.32 (3H, singlet, OCH_3 of methoxymethyl); 3.53 (2H, broad singlet, 2-cephem H_2); 3.98 (3H, singlet, OCH_3 of methoxyimino); 4.23 (2H, quartet, J = 7 Hz, OCH_2CH_3); 4.31 (2H, singlet, CH_2 of methoxymethyl); 5.04 (1H, doublet, J = 6 Hz, 6-cephem H); 5.6–6.3 (5H, multiplet, 7-cephem H, CH_2 of carbonyloxymethyl and NH_2); 6.63 (1H, singlet, 5-thiazole H); 8.13 (1H, doublet, J = 9.0 Hz, 7-cephem NH).

EXAMPLE 21

Isovaleryloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate

The procedure described in Example 20 was repeated to prepare the title compound, having the same properties as the second compound of Example 2.

EXAMPLE 22

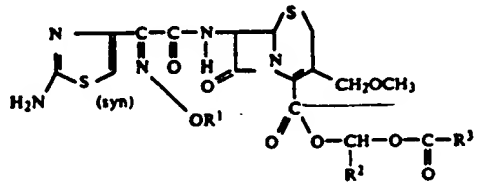
Capsules for oral administration

The following mixture was compounded and encapsulated by conventional means with a No. 2 capsule, to give an encapsulated formulation:

Pivaloyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-(syn)-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate	250 mg
Talc	5 mg
Magnesium stearate	6.7 mg
Sodium laurylsulphate	0.3 mg
Lactose	28 mg

We claim:

1. A compound of the formula



wherein

R^1 is methyl;

R^2 is hydrogen o. methyl;

and

R^3 is a C_1–C_4 alkoxy;

and pharmaceutically acceptable acid addition salts thereof.

2. The compound of claim 1 wherein R^2 is hydrogen.

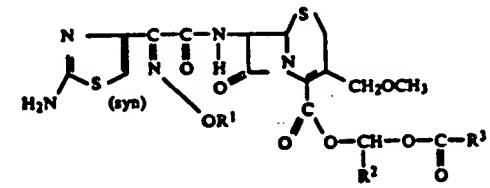
3. The compound of claim 1 wherein R^2 is methyl.

4. The compound of claim 1 wherein R^3 is ethoxy or isopropoxy.

5. The compound of claim 1 or 2 or 3 wherein R^3 is isopropoxy.

6. The compound of claim 1 which is 1-ethoxycarbonyloxyethyl 7-[2-(2-aminothiazol-4-yl)-2-(syn)-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate and pharmaceutically acceptable acid addition salts thereof.

7. A pharmaceutical composition for oral administration comprising an effective amount of an antibiotic in admixture with a pharmaceutically acceptable carrier or diluent, said antibiotic comprising a compound of the formula



wherein

R^1 is methyl;

R^2 is hydrogen or methyl;

and

R^3 is a C_1–C_4 alkoxy;

and pharmaceutically acceptable acid addition salts thereof.

8. The pharmaceutical composition of claim 7 wherein R^2 is hydrogen.

9. The pharmaceutical composition of claim 7 wherein R^2 is methyl.

10. The pharmaceutical composition of claim 7 wherein R^3 is ethoxy or isopropoxy.

11. The pharmaceutical composition of claim 7 or 8 or 9 wherein R^3 is isopropoxy.

12. The pharmaceutical composition of claim 7 wherein said compound is 1-ethoxycarbonyloxyethyl 7-[2-(2-aminothiazol-4-yl)-2-(syn)-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate and pharmaceutically acceptable acid addition salts thereof.

* * * * *

APPENDIX C

Summary of Regulatory Activities

APPENDIX C-1

Summary of Correspondence During IND Period for VANTIN Tablets (Formerly called DOXEF Tablets)

	IND	ANUM	PART	SDATE	PAT_TNUM	RPAGE
1	0000030254	0	BD	7/15/87	7254/87/026	6A/48
2		0	TD	7/15/87	7259/87/012	6A/2085
3		0	TD	7/15/87	7259/87/010	6A/2162
4		0	TD	7/15/87	7263/87/030	6A/2285
5		0	TD	7/15/87	7263/87/047	6A/2318 TOX
6		0	TD	7/15/87	7263/87/033	6A/2332
7		0	TD	7/15/87	7259/87/011	6A/2034
8		0	TD	7/15/87	7263/87/049	6A/1847
9		0	TD	7/15/87	7263/87/041	6A/1472
10		0	TD	7/15/87	7263/87/058	6A/1080
11		0	TD	7/15/87	7263/87/031	6A/2357
12		0	TD	7/15/87	7263/87/034	6A/2450
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	COMM
1	BACTERIOLOGICAL EVALUATION OF CS-807 (U76252): COMPARISON OF IN VITRO ACTIVITY# OF CS-807 W/ACTIVITIES OF OTHER B-L
2	ACTAM ANTIBIOTICS (SANKYO STUDY BR 132-001#), S. OYA ET AL 5/18/87.
3	REPRODUCTION STUDIES OF U76252 (CS807); TERATOGENICITY STUDY (ORAL) IN RATS., #D.L. BLACK, ET AL, STUDY CONDUCTED B
4	Y SANKYO CO., JAPAN, 6/4/87.#
5	TERATOGENICITY STUDY OF U76252 (CS807) GIVEN ORALLY BY GASTRIC INTUBATION TO R#ABBITS, D.L. BLACK, ET AL, STUDY CON
6	DUCTED BY SANKYO CO., JAPAN 6/4/87.#
7	U76252: ACUTE ORAL TOXICITY IN BEAGLE DOGS, R.C. PIPER, ET AL, STUDY CONDUCTED# BY SANKYO CO., JAPAN, 5/26/87.#
8	U76252: TOXICITY STUDY OF CS807 AT HIGH DOSAGE IN DOGS BY ORAL ADMINISTRATION,# R.C. PIPER, ET AL STUDY CONDUCTED B
9	Y SANKYO CO., JAPAN, 6/1/87.#
10	U76252: SIX DAY ORAL RANGE-FINDING STUDY IN FEMALE BEAGLE DOGS, R.C. PIPER, ET# AL, STUDY CONDUCTED BY SANKYO CO.,
11	JAPAN, 6/1/87.#
12	TERATOGENICITY STUDY OF U76252 (RS807) GIVEN ORALLY BY GASTRIC INTUBATION TO R#ATS, D.L. BLACK, ET AL, STUDY CONDUC
13	TED BY SANKYO CO., JAPAN, 6/1/87#
14	U76252: 13 WEEK ORAL TOXICITY STUDY W/4 WEEK RECOVERY GROUPS IN WISTAR-IMAMICH#I RATS. A REPEAT STUDY AT A HIGHER
15	DOSE, R.C. PIPER, ET AL, STUDY CONDUCTED B#Y SANKYO CO., JAPAN, 5/26/87.
16	U76252: 13 WEEK ORAL TOXICITY STUDY W/FOUR WEEK RECOVERY GROUPS IN WISTAR-IMAM#ICHI RATS, R.C. PIPER, ET AL, STUDY
17	CONDUCTED BY SANKYO CO., JAPAN, 6/3/87.#
18	U76252: 3 MONTH ORAL TOXICITY STUDY W/ONE MONTH RECOVERY GROUPS IN FISCHER (F3#44) RATS, R.C. PIPER, ET AL, STUDY C
19	ONDUCTED BY SANKYO CO., JAPAN, 6/1/87.#
20	U76252: 4-WEEK ORAL TOXICITY STUDY IN BEAGLE DOGS, R.C. PIPER, ET AL, STUDY CO#NDUCTED BY SANKYO CO., JAPAN, 5/26/8
21	7.#
22	U76252: 13 WEEK ORAL TOXICITY STUDY IN BEAGLE DOGS, R.C. PIPER, ET AL, STUDY C#ONDUCTED BY SANKYO CO., JAPAN 5/26/8
23	7.#
24	

	IND	ANUM	PART	SDATE	PAT_TRNUM	RPAGE
26	0000030254	0	TD	7/15/87	7263/87/032	6A/849
27		0	TD	7/15/87	7263/87/053	6A/649
28		0	TD	7/15/87	7263/87/029	6A/629
29		0	TD	7/15/87	7263/87/025	6A/609
30		0	TD	7/15/87	7263/87/069	6A/571
31		0	TD	7/15/87	7263/87/026	6A/547
32		0	TD	7/15/87	7263/87/037	6A/522
33		0	TD	7/15/87	7263/87/038	6A/500
34		0	TD	7/15/87	7263/87/046	6A/474
35		0	TD	7/15/87	7263/87/024	6A/451
36		0	TD	7/15/87	7268/87/015	6A/2628
37		0	TD	7/15/87	7268/87/014	6A/2595
38		0	BD	7/15/87	7254/86/037	6A/6
39		0	BD	7/15/87	705/7922/86/003	6A/400
40						
41						
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	COMM
26	U76252: ONE MONTH ORAL TOXICITY STUDY W/ONE MONTH RECOVERY IN WISTAR-IMAMICHI #RATS, R.C. PIPER, ET AL, STUDY CONDU
27	CTED BY SANKYO CO., JAPAN, 6/3/87.#
28	U76252: TWO WEEK ORAL DOSE-FINDING TOXICITY STUDY IN FISCHER (F344) RATS, R.C.# PIPER, ET AL, STUDY CONDUCTED BY SA
29	NKYO CO., JAPAN, 6/1/87.#
30	U76252: ACUTE ORAL TOXICITY IN F344 RATS, R.C. PIPER, ET AL, STUDY CONDCUTED B#Y SANKYO CO., JAPAN, 5/26/87#
31	ACUTE ORAL TOXICITY IN WISTAR-IMAMICHI RATS, R.C. PIPER, ET AL, STUDY CONDUCTE#D BY SANKYO CO. JAPAN, 6/3/87.#
32	A COMPARISON OF THE SENSITIVITY OF THE CECUM OF FISCHER AND WISTAR-IMAMICHI RATS TO COLSTRIDIUM DIFFICILE AND ITS
33	TOXIN, R.C. PIPER, ET AL STUDY CONDUCTED B#Y SANKYO CO. JAPAN, 6/1/87
34	ACUTE INTRAPERITONEAL TOXICITY IN WISTAR-IMAMICHI RATS, R.C. PIPER, ET AL STUD#Y CONDUCTED BY SANKYO CO. JAPAN, 5/2
35	6/87.#
36	ACUTE SUBCUTANEOUS TOXICITY IN WISTAR-IMAMICHI RATS, R.C. PIPER, ET AL, STUDY #CONDUCTED BY SANKYO CO. JAPAN, 6/3/8
37	7.#
38	ACUTE ORAL TOXICITY IN RFVL MICE, R.C. PIPER, ET AL, STUDY CONDUCTED BY SANKYO# CO. JAPAN, 5/26/87#
39	ACUTE INTRAPERITONEAL TOXICITY IN RFVL MICE, R.C. PIPER, ET AL, STUDY CONDUCTE#D BY SANKYO CO. JAPAN 6/1/87#
40	ACUTE SUBCUTANEOUS TOXICITY IN RFVL MICE, R.C. PIPER, ET AL STUDY CONDUCTED BY# SANKYO CO. JAPAN, 6/3/87#
41	EVALUATION OF U76252 (RNH-3746) IN THE IN VITRO CHROMOSOME ABERRATION ASSAY US#ING V79 CELLS IN CULTURE, C.S. AARON
42	, STUDY CONDUCTED BY SANKYO CO., JAPAN, 6/#1/87.
43	EVAULATION OF U76252 (RS807) IN THE SALMONELLA/MICROSOME TEST (AMES-ASSAY) & W#/ESCHERICHIA COLI, C.S. AARON, STUDY
44	CONDUCTED BY SANKYO CO., JAPAN, 6/1/87.#
45	PRELIMINARY IN VITRO ANTIBACTERIAL EVALUATION OF CS-807 (U76252), SANKYO'S ORA#LLY-ACTIVE CEPHALOSPORIN ANTIBIOTIC,
46	G.E. ZURENKO ET AL 6/19/86.#
47	IN VITRO & IN VIVO EVALUATION OF CS-807 AND R3746 AGAINST BACTERIAL PATHOGENS #OF VETERINARY IMPORTANCE, R.J. YANCE
48	Y JR., ET AL6/23/86#
49	

	IND	ANUM	PART	SDATE	PAT_TREUM	RPAGE
51	0000030254	0	BD	7/15/87	7254/86/029	6A/367
52		0	BD	7/15/87	7254/86/116	6A/351
53		0	BD	7/15/87	7254/87/025	6A/332
54		0	BD	7/15/87	7254/86/034	6A/314
55		0	BD	7/15/87	N/A	6A/3
56		0	BD	7/15/87	7254/87/033	6A/251
57		0	BD	7/15/87	7254/87/026	6A/235
58		0	BD	7/15/87	7254/87/030	6A/203
59		0	BD	7/15/87	7254/87/028	6A/164
60		0	MD	7/15/87		2/1
61		0	NP	7/15/87		
62		0	NP	7/15/87		
63		0	MD	7/15/87		5/9
64		0	MD	7/15/87		5/8

	COMM
51	BACTERIOLOGICAL EVALUATION OF CS-807 (U76252): EFFECTS ON EXPERIMENTAL INFECTI$ON IN A CMC-INDUCED POUCH OF RATS (S
52	ANKYO STUDY BR 132-157). Y. AJIKI, ET AL 6#/23/86.
53	A COMP. U76252 (CS-807), CEPHALEXIN, & CEFACLOR ORAL ACT. W/REGARD TP PREVEN. #OF SUBCUTANEOUS ABSC. FORMATION & AN
54	TIBAC. ACTIVITY UPON ESTABLISH. SUBCUTANE#OUS ABSCESS CAUSED BY STAPHY. & STAPHYLOCOCCUS EPIDERMIDIS,CMFORD ETAL 1/>
55	BACTERIOLOGICAL EVALUATION OF CS-807 (U76252): THE THERAPEUTIC EFFECTS AGAINST# SYSTEMIC EXPERIMENTAL INFECTIONS IN
56	MICE (SANKYO BR 132-003), T. MAGARIBUCHI,# ET AL, 5/18/87.
57	IN VIVO EVALUATION OF U76252 (CS-807), J.C. HAMEL, ET AL, 6/2/86.# #
58	MICROBIOLOGY STUDY SYNOPSIS - UPJOHN STUDY# #
59	BACTERIOLOGICAL EVALUATION OF CS-807 (U76252): MORPHOLOGICAL CHANGES CAUSED BY# R3746 (SANKYO STUDY BR 132-036), Y.
60	UTSUI, ET AL, 6/2/87.#
61	BACTERIOLOGICAL EVALUATION OF CS-807 (U76252): ITS BINDING AFFINITIES TO PENIC#ILLIN BINDING PROTEINS OF BACTERIA (
62	SANKYO STUDY BR 132-096), S. OYA ET AL, 5/#18/87.
63	BACTERIOLOGICAL EVALUATION OF CS-807 (U76252): ITS B-LACTAMASE STABILITY AND I#NHIBITORY ACTIVITY (SANKYO STUDY BR
64	132-002), S. OYA ET AL, 5/18/87.#
65	BACTERIOLOGICAL EVALUATION OF CS-807 (U76252): THE EFFECTS OF R-3746 ON THE GR#OWTH CRUVE OF BACTERIA (SANKYO STUDY
66	BR 132-035) Y. UTSUI, ET AL 5/18/87.#
67	COMPLETE LIST OF COMPONENTS OF THE DRUG, INCLUDING ANY REASONABLE ALTERNATIVES# FOR INACTIVE INGREDIENTS.#
68	SEE PROTOCOL R/1140/4911 "COMPARISON OF ORAL U76252 AND CEFACLOR IN THE TREATM#ENT OF COMMUNITY ACQUIRED PNEUMONIA"
69	FOUND ON PG 10A/30 THROUGH 10A/53.#
70	SEE PROTOCOL R/1140/4900 ENTITLE "SINGLE DOSE TOLERANCE AND PHARMACOKINETIC ST#UDIES OF AN ORAL CEPHALOSPORIN ANTIB
71	IOTIC U76252" FOUND ON PG 10A/2 THROUGH 10#A/28. DRUG WILL BE ADMIN ORALLY IN A RANGE OF 100-800 MG.
72	STABILITY DATA ON FORMULATION# #
73	INFORMATION ON PHARMACEUTICAL PROCESSING PLACEBO# #
74	

	IND	ANUM	PART	SDATE	PAT_TRNUM	RPAGE
76	0000030254	0	MD	7/15/87		5/7
77		0	MD	7/15/87		5/4 & 5/5
78		0	MD	7/15/87		5/3
79		0	MD	7/15/87		5/2 & 5/6
80		0	MD	7/15/87		5/1
81		0	MD	7/15/87		4/1
82		0	MD	7/15/87		3/1
83		0	MD	7/15/87		2/2
84		0	BD	7/15/87	N/A	6A/1
85		1	NP	7/22/87		
86						
87		1	NP	7/22/87		
88						
89		2	CD	9/22/87	4800/87/058	7A/1-7A/57
90		2	CD	9/22/87	7256/87/027	9/1-9/132
91						
92		2	NP	9/22/87		
93						
94		4	NP	11/18/87		
95						
96		5	NP	11/25/87		
97						
98						
99						

	COMM
76	INFORMATION ON PHARMACEUTICAL PROCESSING FCT 50 MG AND 100MG U76252 (CS-807)# #
77	GENERAL PROCEDURE TO SUPPORT SEPCIFICATIONS FOR OPADRY X-RAY POWDER DIFFRACTIO#N#
78	NON-COMPENDIAL ITEM OPADRY #YS-1-7075 WHITE# #
79	SPECIFICATIONS AND ANALYTICAL METHODS FOR PLACEBO# #
80	CONTROL INFO: DRUG SUBSTANCE, DRUG PRODUCT, PLACEBO# #
81	DESCRIPTION OF METHOD OF MANUFACTURE # #
82	COMPLETE STATMENT OF QUANTITATIVE COMPOSITION OF THE DRUG INCLUDING ANY REASON#ABLE VARIATIONS EXPECTED DURING THE
83	INVESTIGATIONAL STAGE.#
84	COMPLETE LIST OF COMPONENTS OF THE DRUG, INCLUDING ANY REASONABLE ALTERNATIVE #FOR INACTIVE INGREDIENTS.#
85	BIO EVALUATION SUMMARY - IN VITRO & IN VIVO CHARACTERISTICS# #
86	SEE PROTOCOL R/1140/4910 "COMPARISON OF ORAL U76252 AND CEPHALEXIN IN THE TREA#TMENT OF SKIN AND SOFT TISSUE INFECT
87	IONS" PG 6/1.#
88	SEE PROTOCOL R/1140/4912 "COMPARISON OF ORAL U76252 AND PENICILLIN VK IN TREAT#MENT OF PHARYNGITIS/TONSILLITIS" PG
89	6/56.#
90	"A REVERSED-PHASE HPLC IMPURITIES METHOD FOR U76252 BULK DRUG" 7/8/87.# #
91	"PHARMACOKINETIC SUMMARY OF U76253 SERUM AND URINE DATA FOLLOWING ORAL DOSES O#F U76252 (CS-807) (TO HEALTHY VOLUNTE
92	ERS). SANKYO PHASE I PROTOCOL" 6/19/87#
93	SEE R/1140/4901 "A MULTIPLE DOSE TOLERANCE AND PHARMACOKINETIC STUDY OF TWICE #DAILY DOSING OF AN ORAL CEPHALOSPORI
94	N ANTIBIOTIC U76252 IN HEALTHY VOLUNTEERS"# PG 6A/2 THROUGH 6A/32.
95	SEE R/1140/4903 "THE EFFECTS OF ALTERATION OF GASTRIC PH ON THE PHARMACOKINETI#C PROFILE OF AN ORAL CEPHALOSPORIN A
96	NTIBIOTIC U76252" PG 6A/61 THROUGH 6A/85.#
97	"A MULTIPLE DOSE TOLERANCE & PHARMACOKINETIC STUDY OF THRICE DAILY DOSING OF A#N ORAL CEPHALOSPORIN ANTIBIOTIC U762
98	52 IN HEALTHY VOLUNTEERS" PG 6A/88 THROUGH# 6A/116.
99	

	IND	ANUM	PART	SDATE	PAT_TRNUM	RPAGE
101	0000030254	6	NP	12/30/87		
102		9	NP	3/ 3/88		
103		11	TD	4/21/88	7259/87/018	8/201 - 8/338
104		11	TD	4/21/88	7259/87/019	8/339 - 8/475
105		11	TD	4/21/88	7259/87/012	8/124 - 8/200
106		11	TD	4/21/88	7259/87/010	8/1 - 8/123
107		13	NP	5/18/88		
108		13	MD	5/18/88		7/8
109		13	MD	5/18/88		7/7
110		13	MD	5/18/88		7/6
111		13	MD	5/18/88		7/5
112		13	MD	5/18/88		7/4
113		13	MD	5/18/88		7/3
114		13	MD	5/18/88		7/10
115		13	MD	5/18/88		7/2
116						
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	COMM
101	SEE R/1140/4904 "EFFECTS OF ALTERATION OF GASTRIC MOTILITY ON THE PHARMACOKINE#TIC PROFILE OF AN ORAL CEPHALOSPORIN
102	ANTIBIOTIC U76252" FOUND ON PG 6A/119.#
103	SEE R/1140/4905 "THE EFFECTS OF PROTEIN, FAT & CARBOHYDRATE INTAKE ON THE PHARM#ACOKINETIC PROFILE OF AN ORAL CEPHA
104	LOSPORIN ANTIBIOTIC U76252" SUBMITTED 3/3/88#8.
105	"STUDY OF U76252 (CS807) ADMINISTRATION IN RATS PRIOR TO PREGNANCY AND DURING #THE EARLY STAGE OF PREGNANCY" 12/30
106	/87 ABSTRACT APPEARS ON PGS 8/201 AND 8/20#2
107	"STUDY OF U76252 (CS807) ADMINISTRATION IN RATS DURING THE PRENATAL AND LACTA#TION PERIODS" 12/30/87 ABSTRACT APPE
108	ARS ON PGS 8/339 THROUGH 9/341#
109	"REPRODUCTION STUDIES OF U76252 (CS807); TERATOGENICITY STUDY (ORAL) IN RATS" #6/4/87 ABSTRACT APPEARS ON PGS 8/124
110	THROUGH 8/126#
111	"TERATOGENICITY STUDY OF U76252 (CS807) GIVEN ORALLY BY GASTRIC INTUBATION TO #RABBITS" 6/4/87 ABSTRACT APPEARS ON
112	PGS 8/1 AND 8/2#
113	SEE R/1140/0001 "THE BIOAVAILABILITY OF CEFPO PROX IN HUMANS: EVALUATION OF 50#/100/200MG TABS MANUF BY TOC RELATIV
114	E TO 100MG TABS MANUF BY SANKYO" FOUND ON #PGS 6A/1 THROUGH 6A/24
115	ASSAY VALIDATION DATA# #
116	INGREDIENT SPECIFICATIONS & ANALYTICAL METHODS# #
117	DESC OF MANUFACTURING & PCKGING PROCEDURES# #
118	NAME AND ADDRESS OF MANUFACTURER# #
119	Q/Q COMPOSITION FCT CEFPODOXIME PROXETIL 200MG# #
120	Q/Q COMPOSITION FCT CEFPODOXIME PROXETIL 100MG# #
121	BATCH ANALYSIS; RATIONAL FOR SPECIFICATIONS# #
122	Q/Q COMPOSITION FCT CEFPODOXIME PROXETIL 50MG# #
123	

	IND	ANUM	PART	SDATE	PAT_TRNUM	RPAGE
125	0000030254	16	NP	7/18/88		
126		16	NP	7/18/88		
127		17	NP	8/12/88		
128		17	CD	8/12/88	7214/88/001	9/1-9/313
129		18	MD	9/ 9/88		AR1/31
130		19	TD	9/13/88	7263/87/048	8/108 - 8/148
131		19	TD	9/13/88	7263/87/051	8/149 - 8/255
132		19	TD	9/13/88	7263/87/052	8/256 - 8/428
133		19	TD	9/13/88	7263/87/054	8/429 - 8/470
134		19	TD	9/13/88	7263/87/055	8/471 - 8/496
135		19	TD	9/13/88	7263/87/056	8/497 - 8/516
136		19	TD	9/13/88	7263/87/057	8/517 - 8/554
137		19	TD	9/13/88	7263/87/059	8/555 - 8/829
138		19	TD	9/13/88	7227/88/014	8/830 - 8/841
139		19	TD	9/13/88	7227/88/015	8/842 - 8/855
140		19	CD	9/13/88	7262/87/017	8/25 - 8/49
141						
142						
143						
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	COMM
125	SEE GHBA255 "PHASE II OPEN-LABEL, PARALLEL GROUP, MULTICNTR, DOSE FINDING STUD#Y TO EVALUATE THE SAFETY & EFFICACY
126	OF 3 DOSE LEVELS OF ORALLY ADMIN CEFPODOXI#ME PROXETIL IN PTS W/URINARY TRACT INFECTS PGS 6A/38 THROUGH 6A/100
127	SEE R/1140/0003 "PHARMACOKINETICS OF CEFPODOXIME PROXETIL (U76252) AND BACAMPI#CILLIN IN PLASMA AND SKIN BLISTER FL
128	UID" PGS 6A/1 THROUGH 6A/35#
129	SEE M/1140/0003 "ORAL CEFPODOXIME PROXETIL (U76252) DOSE-RESPONSE STUDY IN THE# TREATMENT OF UNCOMPLICATED GONOCOCC
130	ALURETHRITIS IN MALES" PGS 6A/1 THROUGH 6A#/27
131	"SINGLE DOSE TOLERANCE & PHARMACOKINETIC STUDIES ON AN ORAL CEPHALOSPORIN ANTI#BIOTIC CEFPODOXIME PROXETIL" ABSTRAC
132	T #
133	IMF LETTER# #
134	"ACUTE INTRAVENOUS RABBIT STUDY TO EVALUATE POTENTIAL FOR RENAL TOXICITY" ET A#L 2/29/88#
135	"U76252: 5 WEEK ORAL TOXICITY STUDY IN CYNOMOLGUS MONKEYS" ET AL 2/11/88# #
136	"U76253A: 5 WK IV TOXICITY STY IN F344 RATS" ET AL 2/26/88# #
137	"U76252: 1 WK ORAL TOXICITY STUDY IN CYNOMOLGUS MONKEYS" ET AL 2/15/88# #
138	"U76253: COMPARISON OF THE IMMUNOLOGIC CROSS REACTIVITY, COOMBS 1 TEST AND PRO#TEIN BINDING W/OTHER ANTIBIOTICS" ET
139	AL 2/24/88#
140	"U76252: COMPARATIVE IMMUNOGENICITY WHEN ADMINISTERED TOMICE AND GUINEA PIGS B#Y THE ORAL ROUTE" ET AL 2/22/88#
141	"COMPARATIVE IMMUNOGENICITY WHEN ADMINISTERED TO MICE, GUINEA PIGS, AND RABBIT#S BY THE PARENTERAL ROUTE" ET AL 2/2
142	4/88#
143	"THIRTEEN WK ORAL TOX STDY W/5 WEEK RECOVERY GROUPS IN CYNOMOLGUS MONKEYS" ET #AL 2/9/88#
144	"PRELIMINARY EYE IRRITATION STUDYON U76252 IN ALBINO RABBITS" ET AL 3/1/88# #
145	"PRELIMINARY DERMAL IRRITATION STUDY ON U76252 IN ALBINO RABBITS" ET AL 3/1/88# #
146	"MICROBIOLOGICAL ASSAY FOR THE QUANTITATION OF R3746 (U76253) IN HUMAN PLASMA #AND URINE" ET AL 2/10/88#
147	

	IND	ANOM	PART	SDATE	PAT_TRNUM	RPAGE
149	0000030254	19	CD	9/13/88	7256/87/026	8/3 - 8/24
150		19	CD	9/13/88	7256/88/004	8/50 - 8/73
151		19	CD	9/13/88	7256/87/050	8/74 - 8/107
152		19	CD	9/13/88	7214/88/002	9/2
153		19	NP	9/13/88		
154		19	NP	9/13/88		
155		19	NP	9/13/88		
156		19	NP	9/13/88		
157		20	SD	10/28/88	7214/88/004	9/1 - 9/370
158		20	CD	10/28/88	7214/88/004	9/1 - 9/370
159						
160						
161						

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149	"DETERMINATION OF CS-807 AND ITS METABOLITES IN BODY FLUIDS (A SUMMARY] (SANKY#O STUDY PD-5-133-003) ABSTRACT SEKIN
150	E, M. ET AL 6/16/87#
151	"PLASMA LEVELS OF U76253 IN DOGS DURING A SUBACUTE TOXICITY TEST AFTER ORAL AD#MINISTRATION OF U76252" ET AL 2/3/88
152	#
153	"ABSORPTION, METABOLISM, AND EXCRETION OF RADIOACTIVITY AFTER A SINGLE ORAL AD#MINISTRATION OF U76252 14C TO CYNOMO
154	LYGUS MONKEYS" ET AL 1/11/88#
155	"A MULTIPLE DOSE TOLERANCE AND PHARMACOKINETIC STUDY OF TWICE DAILY DOSING OF# AN ORAL CEPHALOSPORIN ANTIBIOTIC, CE
156	FPODOXIME PROXETIL IN HEALTHY VOLUNTEERS"# ABSTRACT 8/4/88
157	SEE M/1140/0001 "COMPARISON OF ORAL CEFPODOXIME PROXETIL (U76252; CS-807) AND #CEFACLOR (CECLOR) IN TREATMENT OF AC
158	UTE COMMUNITY ACQUIRED PNEUMONIA" PGS 6A/1#2 THROUGH 6A/39.
159	SEE M/1140/0005 "COMP OF ORAL CEFPODOXIME PROXETIL AND PENICILLIN VS POTASSIUM# IN THE TREATMENT OF ACUTE PHARYNGIT
160	IS/TONSILLITIS" PGS 6A/100 THROUGH 6A/124#
161	SEE M/1140/0010 "COMPARISON OF ORAL CEFPODOXIME PROXETIL & CEFACLOR IN TREATME#NT OF ACUTE COMMUNITY ACQUIRED BRONC
162	HITIS" ATTAC PGS 6A/70 THROUGH 6A/99.#
163	SEE M/1140/0008 "COMP OF ORAL CEFPODOXIME PROXETIL AND PENICILLIN V POTASSIUM #IN THE TREATMENT OF ACUTE PHARYNGITI
164	S/TONSILLITIS" PGS 6A/125 THROUGH 6A/149#
165	SEE M/1140/0006 "COMPARISON OF ORAL CEFPODOXIME PROXETIL & CEFACLOR IN THE TRE#ATMENT OF ACTUE COMM ACQUIRED PNEUMO
166	NIA: PGS 6A/40 THROUGH 6A/68.#
167	"A MUTIPLE DOSE TOLERANCE & PHARMACOKINETICS STY OF THRICE DAILY DOSING OF AN #ORAL CEPHALOSPORIN ANTIBIOTIC, CEFPO
168	DOXIME PROXETIL IN HEALTHY VOL" ET AL#
169	"A MULTIPLE DOSE TOLERANCE & PHARMACOKINETICS STUDY OF THRICE DAILY DOSING OF #AN ORAL CEPHALOSPORIN ANTIBIOTIC, CE
170	FPODOXIME PROX IN HEALTHY VOL" GS HUGHES, #JD ORR, DH BATTS
171	

	IND	ANUM	PART	SDATE	PAT_TRNUM	RPAGE
173	0000030254	20	NP	10/28/88		
174						
175		22	NP	11/ 3/88		
176						
177		23	NP	11/23/88		
178						
179		26	SD	2/28/89	7214/88/013	9/1 - 9/264
180		26	CD	2/28/89	7214/88/013	9/1 - 9/264
181						
182		27	NP	3/ 1/89		
183						
184		27	NP	3/ 1/89		
185						
186		28	NP	3/22/89		
187						
188		28	NP	3/22/89		
189						
190		28	SD	3/22/89	N/A	2
191		28	SD	3/22/89	N/A	2
192		28	SD	3/22/89	N/A	2
193		28	SD	3/22/89	N/A	2
194		28	SD	3/22/89	N/A	2
195		28	SD	3/22/89	N/A	2
196						

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173	SEE R/1140/0004 "PHARMACOKINETICS OF CEFPODOXIME PROXETIL (U76252) IN HUMANS W#/IMPAIRED RENAL FUNCTION" PGS 6A/49
174	THROUGH 6A/77.#
175	SEE R/1140/0005 "SINGLE DOSE PROPORTIONALITY & BIOAVAILABILITY OF CEFPODOXIME #AFTER ORAL ADMIN OF 100,200,400,800M
176	G DOSES" PGS 6A/1 - 6A/29#
177	SEE P/1140/0011 "THE EFFECT OF MANUFACTURING PROCESS VARIATIONS ON THE BIOAVAI#LABILITY OF CEFPODOXIME PROXETIL (U7
178	6252) TABS" PGS 6A/2 - 6A/16#
179	RESULTS FOR THE STUDY# #
180	"EFFECTS OF ALTERATION OF GASTRIC PH ON THE PHARMACOKINETIC PROFILE OF THE ORA#L CEPHALOSPORIN ANTI, CEFPODOXIME PR
181	OX" R/1140/4903 2/6/89 ET AL#
182	SEE M/1140/0007 "COMPARISON OF ORAL CEFPODOXIME PROXETIL (U76252; CS-807) AND #CIPROFLOXACIN HYDROCHLORIDE (CIPRO)
183	IN THE TREATMENT OF SKIN AND SOFT TISSUE I#NFECTIONS" PGS 6A/34 - 6A/68
184	SEE M/1140/0002 "COMPARISON OF ORAL CEFPODOXIME PROXETIL (U76252; CS-807) AND #CEFACLOR (CECLOR) IN THE TREATMENT O
185	F SKIN AND SOFT TISSUE INFECTIONS" PGS 6A/#1 - 6A/33
186	SEE P/1140/0022 "ABSORPTION/EXCRETION OF DRUG RELATED RADIOACTIVITY AFTER ORAL# ADMINISTRATION OF U76252 TO HEALTHY
187	VOLUNTEERS" PGS 6A/44 - 6A/76#
188	SEE N/1140/0004 "COMP OF ORAL CEFPODOXIME PROX & CEFTRIAXONE IN THE TREATMENT #OF UNCOMPLICATED GONOCOCCAL INFECTIO
189	N" PGS 6A/12 - 6A/42#
190	STUDY SITE CLOSED DUE TO LACK OF ENROLLMENT 0 PTS ENROLLED# #
191	STUDY SITE CLOSED DUE TO LACK OF ENROLLMENT 0 PTS ENROLLED# #
192	STUDY SITE CLOSED DUE TO LACK OF ENROLLMENT 0 PTS ENROLLED# #
193	STUDY SITE CLOSED DUE TO LACK OF ENROLLMENT 0 PTS ENROLLED# #
194	STUDY SITE CLOSED DUE TO LACK OF ENROLLMENT 0 PTS ENROLLED# #
195	STUDY SITE CLOSED DUE TO LACK OF ENROLLMENT 0 PTS ENROLLED# #
196	

	IND	ANUM	PART	SDATE	PAT_TRNUM	RPAGE
198	0000030254	28	SD	3/22/89	N/A	2
199		28	SD	3/22/89	N/A	2
200		28	SD	3/22/89	N/A	2
201		28	SD	3/22/89	N/A	3
202		28	SD	3/22/89	N/A	3
203		28	SD	3/22/89	N/A	3
204		28	SD	3/22/89	N/A	3
205		28	SD	3/22/89	N/A	3
206		28	SD	3/22/89	N/A	3
207		28	SD	3/22/89	N/A	2
208		28	SD	3/22/89	N/A	2
209		28	SD	3/22/89	N/A	2
210		28	SD	3/22/89	N/A	2
211		28	SD	3/22/89	N/A	2
212		28	SD	3/22/89	N/A	2
213		28	SD	3/22/89	N/A	2
214		28	SD	3/22/89	N/A	2
215		28	SD	3/22/89	N/A	2
216		28	SD	3/22/89	N/A	2
217		28	SD	3/22/89	N/A	2
218		28	SD	3/22/89	N/A	2
219		28	SD	3/22/89	N/A	2
220		28	SD	3/22/89	N/A	
221						

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198	STUDY SITE CLOSED DUE TO COMPLETION OF ENROLLMENT 15 PTS ENROLLED# #
199	STUDY SITE CLOSED DUE TO COMPLETION OF ENROLLMENT 20 PTS ENROLLED# #
200	STUDY SITE CLOSED DUE TO COMPLETION OF ENROLLMENT 15 PTS ENROLLED# #
201	STUDY SITE CLOSED DUE TO LACK OF ENROLLMENT 0 PTS ENROLLED# #
202	STUDY SITE CLOSED DUE TO LACK OF ENROLLMENT 1 PT ENROLLED# #
203	STUDY SITE CLOSED DUE TO LACK OF ENROLLMENT 0 PTS ENROLLED# #
204	STUDY SITE CLOSED DUE TO LACK OF ENROLLMENT 5 PTS ENROLLED# #
205	STUDY SITE CLOSED DUE TO LACK OF ENROLLMENT 0 PTS ENROLLED# #
206	STUDY SITE CLOSED DUE TO LACK OF ENROLLMENT 0 PTS ENROLLED# #
207	STUDY SITE CLOSED DUE TO LACK OF ENROLLMENT 0 PTS ENROLLED# #
208	STUDY SITE CLOSED DUE TO LACK OF ENROLLMENT 1 PT ENROLLED# #
209	STUDY SITE CLOSED DUE TO LACK OF ENROLLMENT 6 PTS ENROLLED# #
210	STUDY SITE CLOSED DUE TO COMPLETION OF ENROLLMENT 21 PTS ENROLLED# #
211	STUDY SITE CLOSED DUE TO COMPLETION OF ENROLLMENT 16 PTS ENROLLED# #
212	STUDY SITE CLOSED DUE TO COMPLETION OF ENROLLMENT 11 PTS ENROLLED# #
213	STUDY SITE CLOSED DUE TO COMPLETION OF ENROLLMENT 40 PTS ENROLLED# #
214	STUDY SITE CLOSED DUE TO LACK OF ENROLLMENT 0 PTS ENROLLED# #
215	STUDY SITE CLOSED DUE TO LACK OF ENROLLMENT 6 PTS ENROLLED# #
216	STUDY SITE CLOSED DUE TO COMPLETION OF ENROLLMENT 20 PTS ENROLLED# #
217	STUDY SITE CLOSED DUE TO COMPLETION OF ENROLLMENT 45 PTS ENROLLED# #
218	STUDY SITE CLOSED DUE TO LACK OF ENROLLMENT 6 PTS ENROLLED# #
219	STUDY SITE CLOSED DUE TO LACK OF ENROLLMENT 12PTS ENROLLED# #
220	
221	

	IND	ANUM	PART	SDATE	PAT_TRNUM	RPAGE
223	0000030254	29	NP	3/23/89		
224		30	NP	3/27/89		
225		31	TD	4/14/89	7227/88/184	8/616 - 8/645
226		31	TD	4/14/89	7227/88/150	8/596 - 8/615
227		31	TD	4/14/89	7227/88/051	8/1 - 8/595
228		31	CD	4/14/89	7256/88/077	9/256 - 9/300
229		31	CD	4/14/89	7256/88/076	9/231 - 9/255
230		31	CD	4/14/89	7214/88/014	9/2 - 9/230
231		32	NP	4/21/89		
232		36	NP	6/ 9/89		
233		36	NP	6/ 9/89		
234		37	NP	6/26/89		
235		37	NP	6/26/89		
236						
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238						
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223	SEE M/1140/0017 "PHASE III, MULTICENTER, OPEN-LABEL PROSPECTIVE STY OF CEFPODO#XIME PROXETIL IN THE TREATMENT OF PT
224	S W/COMPLICATED URINARY TRACT INFECTIONS" #SANKYO 6A/2 - 6A/40
225	SEE M/1140/0016 "PHASE 3 MULTICENTER, DOUBLE BLIND, PARALLEL GROUP, PROSPECTIV#E RANDOMIZED, COMPARATIVE STY OF CEF
226	PODOXIME PROXETIL & AMOXICILLIN IN THE TRT#MT OF OUTPTS W/UNCOMPLICATED URINARY TRACT INFECTS" PGS 6A/2 - 6A/44
227	"EVALUATION OF U76252 IN THE MICRONUCLEUS TEST IN MICE" 2/21/89 C S AARON# #
228	"EVALUATION OF U76252 IN THE AS52/XPRT MAMMALIAN CELL FORWARD GENE MUTATION AS#SAY" 2/1/89 C S AARON#
229	"ONE YR CHRONIC ORAL TOX STY OF CS807 IN RATS" ET AL 1/4/89# #
230	"METHOD VALIDATION OF HAZLETON LABORATORIES AMERICA, INC FOR THE DETERMINATION# OF U76253 (THE ACTIVE METABOLITE OF
231	CEFPODOXIME PROX U76252) IN HUMAN PLASMA"# 10/17/88 ET AL
232	"METHOD VALIDATION OF THE BIODECISION LABORATORIES FOR THE DETERMINATION OF U7#6252 (THE ACTIVE MTEABOLITE OF CEFPO
233	DOXIME PROX) IN HUMAN PLASMA" 10/17/88 ET #AL
234	"EFFECTS OF ALTERATION OF GASTRIC MOTILITY ON THE PHARMACOKINETIC PROFILE OF T#HE ORAL CEPHALOSPORIN ANTIBIOTIC, CE
235	FPODOXIME PROXETIL DOXEF" ET AL 3/2/89#
236	SEE M/1140/0015 "RANDOMIZED COMP STY OF CEFPOD PROX & CEFACLOR IN THE TRTMNT O#F OUTPTS W/UNCOMP URINARY TRACT INFE
237	CTS" PGS 6A/22 - 6A/92#
238	SEE M/1140/0018 "OPEN LABEL EVALUATION OF 2 DOSES OF ORAL CEFPODOXIME PROX IN #THE TRTMNT OF SKIN & SOFT TISSUE INF
239	ECTIONS" PGS 6A/26 - 6A/52#
240	SEE P/1140/0029 "BIOAVAILABILITY OF DOXEF TABS RELATIVE TO COFPODOXIME PROX OR#AL SOLUTION" PGS 6A/54 - 6A/70#
241	DRAFT M/1140/0078 "COMP OF CEFPOD PROX ORAL SUSP (100MG/5ML)(DOXEF) & PENICILL#IN V POTASSIUM ORAL SUSP (250MG/5ML)
242	IN TRTMNT OF ACUTE STREPTOCCAL PHARYNGITI#S/TONSILLITIS IN INFANTS & CHILDREN" 143 - 173
243	DRAFT M/1140/0027 "COMP OF CEFPOD PROX OS (100MG/5ML)(DOXEF)& PENICILLIN V POT#ASS OS (250MG/5ML)IN TRTMNT OF ACUTE
244	STREPTOCOCCAL PHARYNGITIS/TONSILLITIS IN #INFANTS & CHILDREN" PGS 112-142
245	

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247	0000D30254	37	NP	6/26/89		
248		37	NP	6/26/89		
249		37	NP	6/26/89		
250		40	NP	8/18/89		
251		39	NP	8/18/89		
252		41	TD	8/22/89	7227/89/065	8/1 - 8/16
253		44	SD	10/25/89	7214/89/012	44
254		44	CD	10/25/89	7214/89/012	42-224
255		44	BD	10/25/89	7252/88/092	9-15
256		44	BD	10/25/89	7252/89/001	16-41
257		44	BD	10/25/89	7252/88/031	1-8
258		45	SD	11/ 7/89	N/A	AR2/6-AR2/8
259		45	SD	11/ 7/89	N/A	AR2/6-AR2/8
260		45	SD	11/ 7/89	N/A	AR2/6-AR2/8
261		45	SD	11/ 7/89	N/A	AR2/6-AR2/8

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247	DRAFT PROT M/1140/0020 "COMP OF CEFPODOXIME PROXETIL ORAL SUSPENSION (100MG/5M$L) VS TRIMETHOPRIM/SULFAMETHOXAZOLE
248	(BACTRIM) ORAL SUSP (40MG TRIMETHOPRIM & 2$0MG SULFAMETHOXAZOLE/5ML)IN TRTMNT OF UNCOMP URINARY INFECTS INFANTS &C>
249	DRAFT PROT M/1140/0014 "COMP OF ORAL CEFPOD PROX ORAL SUSP (100MG/5ML) VS AMOX$ICILLIN/CLAVULANATE POTASSIUM ORAL S
250	USP (250MG/5ML) IN TRTMNT OF ACUTE SUPPURA$TIVE OTITIS MEDIA IN INFANTS & CHILDREN" PGS 38 - 74
251	DRAFT PROT M/1140/0013 "COMP OF CEFPOD PROX ORAL SUSP (100MG/5ML) VS AMOXICILL$IN/CLAVULANATE POTASSIUM ORAL SUSP (
252	250MG/5ML) IN TRTMNT OF ACUTE SUPPURATIVE $OTITS MEDIA IN INFANTS & CHILDREN" PGS 1 -37
253	SEE M/1140/0025 "OPEN LABEL EVALUATION OF CEFPOD PROX (400MG BID) IN TRTMNT OF$ CAMPYLOBACTER PYLORI INFECTION OF T
254	HE UPPER GASTROINTESTINAL TRACT" PGS 6A/2 $- 6A/19 OF THIS SUB
255	SEE P/1140/0031 "BIOAVAILABILITY OF DOXEF FG RELATIVE TO DOXEF TABS IN NORMAL $VOLUNTEERS" PGS 6A/2 - 6A/18 OF THIS
256	SUB$
257	"EVALUATION OF U76252 IN THE IN VITRO UNSCHEDULED DNA SYNTHESIS ASSAY IN RAT P$RIMARY HEPATOCYTES$" ET AL 6/8/89
258	SEE TR FOR FULL REPORT$ $
259	"EFFECTS OF PROTEIN, FAT & CARBOHYDRATE INTAKE ON PHARMACOKINETIC PROFILE OF T$HE ORAL CEPHALOSPORIN ANTIBIOTIC, CE
260	FPOD PROX, DOXEF FCT" GS HUGHES ET AL 5/4/$89
261	"CEFPOD PROX AN ORALLY ACTIVE CEPHALOSPORIN: IN VITRO ACTIVITY AGAINST ANTIBIO$TIC-RESISTANT NEISSERIA GONORRHOEAE"
262	ET AL 11/22/89$
263	"CAMPYLOBACTER PYLORI: TOXIN PRODUCTION & ANTIMICROBIAL SUSCEP" ET AL 2/21/89 $EDITED$
264	"ACTIVITY OF ANTIBIOTICS (INCLDING CEFMET, PALDIMYCIN,TROSP,SPECTON,& CEFPOD P$ROX (CS807) AGAINST RECENT CLIN ISOL
265	ATES OF BRANHAMELLA CATARRHALIS" GH YAGI G$E ZURENKO 5/18/88 EDITED
266	STY COMPLETED. FINAL REPORT PENDING$ $
267	STY COMPLETED. FINAL REPORT PENDING$ $
268	STY COMPLETED. FINAL REPORT PENDING$ $
269	STY COMPLETED. FINAL REPORT PENDING$ $

	IND	ABBR	PART	SDATE	PAT_TREAT	RPAGE
272	0000030254	15	SD	11/ 7/89	N/A	AR2/6-AR2/8
273		15	SD	11/ 7/89	N/A	AR2/6-AR2/8
274		15	SD	11/ 7/89	N/A	AR2/6-AR2/8
275		15	SD	11/ 7/89	N/A	AR2/6-AR2/8
276		15	SD	11/ 7/89	N/A	AR2/6-AR2/8
277		15	SD	11/ 7/89	N/A	AR2/6-AR2/8
278		15	SD	11/ 7/89	N/A	AR2/6-AR2/8
279		15	SD	11/ 7/89	N/A	AR2/9
280		15	SD	11/ 7/89	7214/88/014	R2/1
281		15	SD	11/ 7/89	N/A	AR2/6-AR2/8
282		15	SD	11/ 7/89	N/A	AR2/6-AR2/8
283		15	SD	11/ 7/89	N/A	AR2/6-AR2/8
284		15	SD	11/ 7/89	N/A	AR2/11
285		15	SD	11/ 7/89	N/A	AR2/2
286		15	SD	11/ 7/89	N/A	AR2/4
287		15	SD	11/ 7/89	N/A	AR2/4
288		15	SD	11/ 7/89	N/A	AR2/4
289		15	SD	11/ 7/89	N/A	AR2/4
290		15	SD	11/ 7/89	N/A	AR2/4
291		15	SD	11/ 7/89	N/A	AR2/4
292		15	SD	11/ 7/89	N/A	AR2/4
293		15	SD	11/ 7/89	N/A	AR2/4
294		15	SD	11/ 7/89	N/A	AR2/4
295						

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272	STY COMLETED. FINAL REPORT PENDING# #
273	STY COMPLETED. FINAL REPORT PENDING# #
274	STY COMPLETE. FINAL REPORT PENDING# #
275	STY COMPLETED. FINAL REPORT PENDING# #
276	STY COMPLETED. FINAL REPORT PENDING# #
277	STY COMPLETED. FINAL REPORT PENDING# #
278	STY COMPLETED. FINAL REPORT PENDING# #
279	STY IS CLINIC COMP & ANALYSIS OF DATA IS IN PROGRESS# #
280	SEE TR FOR COMP REPORT# #
281	STY COMPLETED. FINAL REPORT PENDING# #
282	STY COMPLETED. FINAL REPORT PENDING# #
283	STY COMPLETED. FINAL REPORT PENDING# #
284	STY IS CLINIC COMP & ANALYSIS OF DATA IS IN PROGRESS# #
285	SEE PG FOR RESULTS# #
286	STY COMPLETED. FINAL REPORT PENDING# #
287	STY COMPLETED. FINAL REPORT PENDING# #
288	STY COMPLETED. FINAL REPORT PENDING# #
289	STY COMPLETED. FINAL REPORT PENDING# #
290	STY COMPLETED. FINAL REPORT PENDING# #
291	STY COMPLETED. FINAL REPORT PENDING# #
292	STY COMPLETED. FINAL REPORT PENDING# #
293	STY COMPLETED. FINAL REPORT PENDING# #
294	STY COMPLETED. FINAL REPORT PENDING# #
295	

	IND	ANUM	PART	SDATE	PAT_TRNUM	SPAGE
297	0000030254	45	SD	11/ 7/89	N/A	AR2/4
298		45	SD	11/ 7/89	N/A	AR2/4
299		45	SD	11/ 7/89	N/A	AR2/10
300		45	SD	11/ 7/89	7214/88/004	AR2/1
301		45	MD	11/ 7/89		AR2/65 - AR2/67
302		45	SD	11/ 7/89	7214/88/001	AR2/1
303		45	SD	11/ 7/89	7214/88/002	AR2/1
304		45	SD	11/ 7/89	N/A	AR2/4
305		45	SD	11/ 7/89	N/A	AR2/4
306		45	SD	11/ 7/89	N/A	AR2/4
307		45	SD	11/ 7/89	N/A	AR2/4
308		45	SD	11/ 7/89	N/A	AR2/4
309		45	SD	11/ 7/89	N/A	AR2/5
310		45	SD	11/ 7/89	N/A	AR2/5
311		45	SD	11/ 7/89	N/A	AR2/5
312		45	SD	11/ 7/89	N/A	AR2/5
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314		45	SD	11/ 7/89	N/A	AR2/5
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316		45	SD	11/ 7/89	N/A	AR2/5
317		45	SD	11/ 7/89	N/A	AR2/5
318		45	SD	11/ 7/89	N/A	AR2/5
319		45	SD	11/ 7/89	N/A	
320						

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297	STY COMPLETED. FINAL REPORT PENDING# #
298	STY COMPLETED. FINAL REPORT PENDING# #
299	STY IS CLINIC COMP & ANALYSIS OF DATA IS IN PROGRESS# #
300	SEE TR FOR COMP REPORT# #
301	LETS REF SANKYO'S DMF (NO # GIVEN) FOR CEFPOD PROX & SANKYO'S DMF (#6937) FOR #CEFPOD PROX PCT ARE ATTACHED#
302	SEE TR FOR COMPLETE REPORT# #
303	SEE TR FOR COMPLETE REP# #
304	STY COMPLETED. FINAL REPORT PENDING# #
305	STY COMPLETED. FINAL REPORT PENDING# #
306	STY COMPLETED. FINAL REPORT PENDING# #
307	STY COMPLETED. FINAL REPORT PENDING# #
308	STY COMPLETED. FINAL REPORT PENDING# #
309	STY COMPLETED. FINAL REPORT PENDING# #
310	SEE PG FOR SYNOPSIS OF REP# #
311	STY COMPLETED. REPORT PENDING# #
312	STY COMPLETED. FINAL REPORT PENDING# #
313	STY COMPLETED. REPORT PENDING# #
314	STY COMPLETED. REPORT PENDING# #
315	STY COMPLETED. REPORT PENDING# #
316	STY COMPLETED. REPORT PENDING# #
317	STY COMPLETED. REPORT PENDING# #
318	STY COMPLETED. REPORT PENDING# #
319	STY COMPLETED. REPORT PENDING# #
320	

	IND	ANUM	PART	SDATE	PAT_TREUM	RPAGE
322	0000030254	45	SD	11/ 7/89	N/A	AR2/4
323		45	SD	11/ 7/89	N/A	AR2/4
324		45	SD	11/ 7/89	N/A	AR2/4
325		45	SD	11/ 7/89	N/A	AR2/4
326		45	SD	11/ 7/89	N/A	AR2/4
327		45	SD	11/ 7/89	N/A	AR2/4
328		45	SD	11/ 7/89	N/A	AR2/4
329		45	SD	11/ 7/89	N/A	AR2/4
330		45	SD	11/ 7/89	N/A	AR2/4
331		45	SD	11/ 7/89	N/A	AR2/4
332		45	SD	11/ 7/89	N/A	AR2/4
333		45	SD	11/ 7/89	N/A	AR2/4
334		45	SD	11/ 7/89	N/A	AR2/4
335		45	SD	11/ 7/89	N/A	AR2/4
336		45	SD	11/ 7/89	N/A	1-500
337		47	SD	11/ 9/89	7214/89/027	1-500
338		47	CD	11/ 9/89	7214/89/027	
339						
340		49	NP	11/28/89		
341		81	TD	1/14/90	7227/89/072	620 - 691
342		81	TD	1/14/90	7227/89/084	692 - 851
343		81	TD	1/14/90	7227/90/040	1-68
344						

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322	STY COMPLETED. FINAL REPORT PENDING# #
323	STY COMPLETED. FINAL REPORT PENDING# #
324	STY COMPLETED. FINAL REPORT PENDING# #
325	STY COMPLETED. FINAL REPORT PENDING# #
326	STY COMPLETED. FINAL REPORT PENDING# #
327	STY COMPLETED. FINAL REPORT PENDING# #
328	STY COMPLETED. FINAL REPORT PENDING# #
329	STY COMPLETED. FINAL REPORT PENDINPG# #
330	STY COMPLETED. FINAL REPORT PENDING# #
331	STY COMPLETED. FINAL REPORT PENDING# #
332	STY COMPLETED. FINAL REPORT PENDING# #
333	STY COMPLETED. FINAL REPORT PENDING# #
334	STY COMPLETED. FINAL REPORT PENDING# #
335	STY COMP. FINAL REPORT PENDING# #
336	STY COMPLETED. FINAL REPORT PENDING# #
337	SEE TR FOR REPORT# #
338	"PHARMACOKINETICS OF CEFPOD & AMPICILLIN IN PLASMA & SKIN BLISTER FLUID FLLWING ORAL DOSING OF CEFPOD PROX TABS &
339	BACAMPICILLIN TABS" GS HUGHES ET AL 10/12/#89 (R/1140/0003)
340	SEE P/1140/0033 "PHARMACOKINETICS OF CEFPOD IN HEMODIALYSIS PTS FLLWING ADMIN #OF DOXEF TABS" PGS 2-18 OF THIS SUB#
341	"U76252 ONE MONTH ORAL TOXICITY STUDY IN INFANT DOGS"# #
342	"FOUR WEEK ORAL TOXICITY STUDY IN INFANT WISTAR-IMAMICHI RATS"# #
343	"U76252: ACUTE ORAL TOXICITY STUDY OF AN IMPURITY DEGRADATION BY-PRODUCTS AND #HEAT DEGRADED U-76252 IN RFVL MICE"#
344	

	IND	ANUM	PART	SDATE	PAT_TRNUM	RPAGE
346	0000030254	81	TD	1/14/90	7227/90/041	101 - 144
347						
348		81	TD	1/14/90	7227/90/035	145 - 339
349		81	TD	1/14/90	7224/90/041	340 - 381
350		81	TD	1/14/90	7224/90/040	382-422
351		81	TD	1/14/90	7227/90/042	69 - 100
352		81	TD	1/14/90	7227/90/043	439 - 473
353		81	TD	1/14/90	7227/90/044	474 - 517
354		81	TD	1/14/90	7227/89/071	518 - 540
355		81	TD	1/14/90	7227/89/078	541 - 619
356		81	TD	1/14/90	7228/90/061	423 - 438
357						
358		54	SD	3/ 9/90	7256/89/030	1/172 - 1/269
359						
360		54	SD	3/ 9/90	7215/89/054	2/1-2/916
361						
362		54	TD	3/ 9/90	7228/89/019	1/18 - 1/34
363		54	CD	3/ 9/90	7256/89/081	1/103 - 1/171
364		54	CD	3/ 9/90	7224/90/009	1/135 - 1/102
365						
366		54	CD	3/ 9/90	7256/89/030	1/172 - 1/269
367						
368						

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346	"AN ACUTE INTRAVENOUS TOXICITY STUDY IN RABBITS TO EVALUATE THE NEPHROTOXIC PO#TENTIAL OF 400 AND 800 MG/KG U76253A
347	"#
348	"U76252 SIX MONTH ORAL TOXICITY STUDY INN BEAGLE DOGS"# #
349	"TERATOGENICITY STUDY OF U76252 (CS807) IN RABBITS (FIRST PRELIMINARY STUDY)"# #
350	"TERATOGENICITY STUDY OF U76252 (CS807) IN RABBITS (SECOND PRELIMINARY STUDY)"# #
351	"AN ACUTE INTRAVENOUS TOXICITY STUDY IN RABBITS TO EVALUATE THE NEPHROTOXIC JP#OTENTIAL OF 200 MG/KG U76253A"#
352	"ANTIGENICITY EVALUATION U76252 IN COMBINATION WITH FREUND'S COMPLETE ADJUVANT# IN JAPANESE ALBINO RABBITS"#
353	"ANTIGENICITY EVALUATION OF HEAT DEGRADED U76252 IN JAPANESE ALBINO RABBITS"# #
354	"ACUTE TOXICITY STUDY OF CS-807 IN INFANT RATS (WISTAR-IMAMICHI) WITH ORAL ADM#INISTRATION"#
355	"ONE MONTH ORAL TOXICITY STUDY IN INFANT DOGS (SUPPLEMENTAL STUDY AT LOWER DOS#ES)"#
356	"EVALUATION OF U76252 (RS-807) FOR THE INDUCTION OF MITOTIC RECOMBINATION OR G#ENE CONVERSION IN THE YEAST SACCHARO
357	MYCES CEREVISIAE (STRAIN XS-2316)#
358	"SINGLE DOSE TOLERANCE & PHARMACOKINETIC STYS OF AN ORAL CEPHALOSPORIN ANTIBIO#TIC U76252 IN HLTHY VOLUNTEERS" DRUG
359	ANALYSIS RESULTS OF CEFPOD PROX IN HUMAN #URINE FOR PROT.
360	"SINGLE DOSE PHARMACOKINETICS OF CEFPOD PROX FLLWING ORAL ADMIN OF CEFPOD PROX# TABS" REP OF PHARMACOKINETICS OF CE
361	FPOD FLLWING SINGLE DOSE ADMIN IN 39 HLTHY# VOLUNT IN 100-800MG 1/12/90
362	"EVALUATION OF U76252 IN SALMONELLA/MICROSOME TEST (AMES ASSAY)" 12/20/89 CS A#ARON ET AL#
363	"QUANTITATION OF CEFPODOXIME (U75253) IN PLASMA" 11/1/189 ME ROYER# #
364	"U76252: SEGMENT I FERTILITY & GENERAL REPRODUCTIVE PERFORMANCE STY (ORAL) IN #THE RAT" DF MORRIS TA MARKS ET AL 2/
365	19/90#
366	"SINGLE DOSE TOLERANCE & PHARMACOKINETIC STYS OF AN ORAL CEPHALOSPORIN ANTIBIO#TIC U76252 (CS-807) IN HEALTHY VOLUN
367	TEERS" KS BOTHWELL STY RESULTS R/1140/4900#
368	

	IND	ANUM	PART	SDATE	PAT_TRNUM	RPAGE
370	0000030254	54	CD	3/ 9/90	7215/89/054	2/1 - 2/916
371		57	MD	4/12/90		36
372		57	MD	4/12/90		35
373		57	MD	4/12/90		34
374		57	MD	4/12/90		31-33
375		57	MD	4/12/90		3
376		57	MD	4/12/90		29-30
377		57	MD	4/12/90		28
378		57	MD	4/12/90		27
379		57	MD	4/12/90		24-26
380		57	MD	4/12/90		37
381		57	MD	4/12/90		38
382		57	MD	4/12/90		39
383		57	MD	4/12/90		4
384		57	MD	4/12/90		40
385		57	MD	4/12/90		41
386		57	MD	4/12/90		5
387		57	MD	4/12/90		6
388		57	MD	4/12/90		7
389		57	MD	4/12/90		8
390		57	MD	4/12/90		9
391		57	MD	4/12/90		23
392		57	MD	4/12/90		
393						

	COMM
370	"SINGLE DOSE PHARMACOKINETICS OF CEFPOD PROX FLLWING ORAL ADMIN OF CEFPOD PROX# TABS" STY RESULTS R/1140/4900 MT BO
371	KIN ET AL 1/12/90#
372	DESC OF TESTS AND EMPTY GELATIN CAPS# #
373	INGRED SPECS FOR HFC (CT) PENICILLIN VPOTASSIUM 250MG# #
374	CONTROL T/A PROCEDURE 4529 REV 5.02# #
375	CONTROL T/A PROCEDURE 4490 REV 5.02 COLOR DIFFERENCE FOR TABLET COATING MATERI#AIS#
376	COMP LIST OF COMPONETS & QUANTITATIVE COMPOSITION OF DRUG KEFLEX PULVULES 500M#G#
377	GENERAL PROCEDURE GP 373 REV 6.02 XRAY POWDER DIFRACTION# #
378	REGIS SPECS EDP NO. 158116 REV 2.02# #
379	T/A PROCEDURE 9251 REV 5.00# #
380	GENERAL PROCEDURE GP 006 REV 6.02# #
381	INGREDIENT SPECS FOR HFC (HFC) AMOXICILLIN 250MG# #
382	INGREDIENT SPECS FOR HFC PLACEBO# #
383	DESC OF TESTS FOR PLACEBO FORMULATIONS# #
384	COMP LIST OF COMPONENTS & QUANTITATIVE COMPOSITION OF DRUG HFC (HFC) AMOXICILL#IN 250MG#
385	PROT OF ASSAY; CEFPOD PROXETIL FCT 100MG# #
386	PROT OF ASSAY CEFPODOXIME PROX FCT 100MG# #
387	COMP LIST OF COMPONENTS & QUANTITATIVE COMP OF DRUG HFC PLACEBO# #
388	INFO ON PHARMACEUTICAL PROCESSING & PACKAGING FCT CEFPODOXIME 100MG# #
389	INFO ON PHARMACEUTICAL PROCESSING & PCKGING HFC (CT) PENICILLIN V POTASSIUM 25#0MG#
390	INFO ON PHARMACEUTICAL PROCESSING & PCKGING KEFLEX PULVULES 500MG# #
391	INFO ON PHARMACUETICAL PROCESSING & PCKGING HFC (HFC) AMOXICILLIN 250MG# #
392	T/A PROCEDURE 0306 REV 5.00# #
393	

	IND	ANUM	PART	SDATE	PAT_TRNUM	RPAGE
395	0000030254	57	MD	4/12/90		22
396		56	NP	4/12/90		
397						1
398		57	MD	4/12/90		10
399		57	MD	4/12/90		11
400		57	MD	4/12/90		12
401		57	MD	4/12/90		13
402		57	MD	4/12/90		2
403		57	MD	4/12/90		
404		60	NP	5/17/90		
405		64	NP	7/ 6/90		
406		66	TD	7/20/90	7256/89/016	6/1 - 6/238
407						
408		66	TD	7/20/90	7256/89/071	6/239 - 6/294
409						
410		66	TD	7/20/90	7256/89/067	6/1417 - 6/2591
411						
412		66	TD	7/20/90	7215/89/058	6/295
413						1 - 55
414		70	MD	8/30/90		
415		72	NP	10/ 2/90		
416		74	NP	11/ 7/90		
417		76	NP	11/21/90		
418						

	COMM
395	REGIS SPECS: EDP NO 106250 REV 2.03# #
396	SEE P/1140/0036 "BIOAVAILABILITY COMP OF CEFPOD PROX 200MG TABS MANUFACTURED B#Y ROUSSEL UCLAF & TUC?GS 1-15 OF T
397	HIS SUB OF 4/13/90#
398	COMP LIST OF COMPONENTS & QUANTITATIVE COMP OF DRUG, FCT CEFPODOXIME 100MG# #
399	INFO ON PHAMACEUTICAL PROCESSING & PCKGING HFC PLACEBO# #
400	INGREDIENT SPECS FOR FCT CEFPODOXIME 100MG# #
401	REGIS SPECS: EDP NO. R247 REV 2.00# #
402	T/A CONTRAL PROCEDURE 7RD57 REV 5.02##
403	COMPLETE LIST OF COMPONENTS & QUANTITATIVE COMPOSITION OF DRUG HFC (CT) PENICI#LLIN V POTASSIUM 250#
404	# #
405	# #
406	"THE BIOAVAILABILITY OF CEFPODOXIME PROXETIL (76252) IN HUMANS: EVALUATION OF #50 MG, 100MG AND 200# TABS MANUFACT
407	URED BY TUC RELATIVE TO 100MG TABS MANUFAC#TURED BY SANKYO" PROTOCOL R1150-0001
408	"A MULTIPLE DOSE TOLERANCE AND PHARMACOKINETIC STUDY OF TWICE DAILY DOSING OF #AN ORAL CEPHALOSPORIN ANTIBIOTIC IN
409	HEALTHY VOLUNTEERS" PROTOCOL R1140-4901#
410	"A MULTIPLE DOSE TOLERANCE AND PHARMACOKINETIC STUDY OF THRICE DAILY DOSING OF# AN ORAL CEPHALOSPOR ANTIBIOTIC U7
411	6252 IN HEALTHY VOLUNTEERS"#
412	"MULTIPLE-DOSE PHARMACOKINETICS OF CEFPODOXIME FOLLOWING TWICE DAILY ORAL ADMI#NISTRATION OF CEFPODIME PROXETIL T
413	ABLETS" 10/7/87#
414	COMPONENTS, COMPOSITION, STABILITY AND CONTROL# #
415	# #
416	# #
417	# #
418	

DOXEF® Tablets, Cefpodoxime Proxetil

IND 30,254

JRB 3-9-90 Amendment 054
Submitted Item 6 M1140/0002 Puopolo, M/1140/0006 Mullenix, Revision M/1140/0004 Libertin, New subinvestigators, M1140/0007 Tregor study closure, Mark Todd added as a clinical monitor, Corrections to previous submissions, Part 8 TR 7228/89/019 Ames Assay, TR 7224/90/009 Oral Rat, Clinical TR7256/89/081 HPLC TR 7256/89/030 Protocol 4900 TR 7215/89/054 Protocol R/1140/4900

RWL 3-20-90 Amendment 055
Request meeting to discuss whether a computer assisted NDA review system would be useful with NDA

RED 4-13-90 Amendment 056
Item 6, P/1140/0036 Hughes, M1140/0001 Phillips, M/1140/0005 Deeter, M/1140/0006 Koller, Braun, Farber, M/1140/0018 Hooker, M/1140/0004 Amendment Schlossberg, New Subinvestigators, Corrections

RED 4-12-90 Amendment 057
Item 7 Manufacturing and Control info UPDATE

RWL 4-6-90 Amendment 058
Confirms meeting of 4-19-90 at 10:00 a.m. per telephone conversations

JAE 4-20-90
Request a *preNDA meeting to discuss the content and scope of theNDA, etc.

RWL 5-16-90 Amendment 59
Provided prototypes of data displays for screens re CANDA per request

JAE 5-17-90 A 60-0001 & 0002 Amend., 0034 new Johnson 0007-

JAE 5-23-90 #61
Submitted additional info on the Statistical Analysis plans in preparation for our Pre-NDA filing meeting on 6-18-90

JAE 7-6-90 A#63
Submitted revised Efficacy Master Tables as discussed during PreNDA meeting

JAE 7-6-90 A#62
Submitted Safety Report from Japan with events serious and unexpected

JAE 7-10-90 A#65
Submitted Safety report with event from Japan which was serious and unexpected

JAE 7-6-90 Amendment #064
Submitted Part 6/1-22 Protocol P/1140/0041 Tompkins, Protocol M/1140/0001 Rich 6/23-25, Protocol M/1140/0006 6/26-30 Bailey; 6/31-41 Amendments, Part 7/1 Labeling for P/1140/0041

DOXEF® Tablets, Cefpodoxime Proxetil IND 30,254

RWL 7-18-90
Request comments re M/1140/0043, 0044 & 0045 prior to formal submission from Dr. Susan Alpert per request

CPE 7-25-90 Amendment #067
Submitted Safety Report from Japan where marketed

JAE 8-3-90 Amendment #068
Submitted modified tables for review and a brief summary of telephone conversation of 7-17-90

JAE 8-7-90
Submitted several journal articles we failed to include with our 7-18-90 letter

JAE 8-30-90 A#70
Part 7 1-55 Components, Composition, Stability & Control

JAE 9-17-90 A#71
Submitted Annual Report

JAE 9-21-90 A#71
Corrects number of 9-17-90 amendment to #71

CCE 7-20-90 A#66
Submitted Part 6 TR 7256/89/016 Protocol R1140-0001, 6/239-294 TR 7256/89/071 $1140-4901, 6/295-1416 TR7215/89/058 6/1417-2591 TR7256/89/067 see 2-7-91 Addendum

JAE 11-5-90
Ask to submit our tradename to FDA's labeling and Nomenclature Committee for an assessment of our tradename

11-7-90 new 0045 Miller, Klimas, Harper, Dennington 0046 Weidenbach termination abol

JAE 11-21-90 A#75
Submitted Safety Report re case from Japan re tonsilitis & hemorrhagic colitis

JAE 11-21-90 A#76
Submitted protocol P/1140/0037 & Labeling for M. Allen Tompkins

JAE 8-23-90 A#69
Submitted Part 6 Change in Protocol P-1140/0041 M. Allen Tompkins, and adds Herbert A. Moskow to Protocol M1140/0001

JAE 10-10-90 A#73
Submitted Part 6/1-5 Degelau Protocol P/1140/0046, 6/6 Change in Protocol M1140/0008 Kopel, Kazmierowski, Clower, Tucker, Allen, Stone

JAE 12-20-90 A#77
Submitted IND Safety Report thrombocytosis/w high platelet count

JAE 12-21-90 A#78
Part 6/1-7 Milko Protocol M1140/0045,, 6/8-11 TR 9155/90/016, 6/12-13 TR 9155/90/024, 6/14-16 TR 7214/90/0007

x JAE 10-2-90 #072 Prot M1140/0046 1-49 Woodruff, 0006 Curry 50-54 Labeling

VANTIN® Tablets, Cefpodoxime Proxetil IND 30,254, (name change from Doxef 4/27/92)

1-3-91 Submitted A#79 Protocol M/1140/0048 1-43, David L. Smith, Protocol M/1140/0045 Mansfield and subs 44-59, Protocol M/1140/0046 Hines & subs 60-62, Moskow & sub 63-65, Stevens 66 -79, Moreno 80-88, Butler 89-95, list of subs for prior protocols, changes in protocols M1140/0004, M1140/0008, M1140/0046, M1140/0037, M1140/0006 Part 7 labeling for Protocol M/1140/0048 pages 100-102

1-9-91 A#80 Submitted Safety Report

1-11-91 Notified that on 11-6-90 we provided FDA with four diskettes containing examples of the type of submission we are planning, Data Base Reference Manual and User Guide & ZyIndex Manual. NDA submission dates is 3-29-91

1-14-91 A#081 Submitted Acute Toxicity Studies: TR's 7227/90/040, 7227/90/042, 7227/90/041, Multi-Dose Toxicity studies TR 7227/90/035, Reproduction Studies TR 7224/90/041, 7224/90/040, Mutagenicity Studies TR 7228/90/061, Other Studies TR 7227/90/043 7227/90/044, Special Toxicity Studies TR 7227/89/071, 7227/89/078, 7227/89/072, 7227/89/084

1-16-91 A#082 Submitted Part 6 TR's 7256/90/032, 1-66; 7215/90/033,67-82; 7256/89/078,83-156; 7215/90/017,157-187; 7256/89/087,188-220; 7215/90/023, 221-247; 7256/89/075,248-292; 7215/90/030,293-309; 7256/90/047,1-54 vol.2; 7215/90/034,55-59; 7256/89/027,70-173; 7215/90/026,174-191; 7215/90/037,192-571

1-18-91 A#83 Submitted TRs (ADME) 6/1-11 7256/90/073, 6/12-25 7256/90/074, 29-67 7256/87/040, 68-84 7256/90/069, 85-97 7256/90/070, 98-116 7256/90/067, 117-144 7256/90/079, 145-180 7256/90/065, 181-214 7156/87/053, 215-245 7256/90/084, 246-269 7256/88/004, 270-313 7256/90/068, 314-329 7256/90/075, 330-343 7256/90/077, 344-352 7256/90/066, 353-373 7256/90/071, 374-386 7256/90/078, 387-427 7256/90/072, 428-447 7256/90/076, Pharmacology: 448-479 TR 7254/90/076, 480-485 7252/88/013, 486-497 705-7922-88-014, 498-508 7252/88/049, 509-543 7224/90/055, 544-552 7224/90/056, 553- TR 7224/90/057

1-22-91 A#084 Submitted Part 6/1-41 Protocol M/1140/0050, Kearley & subs, Hutchens & subs, Marmorstein, Stone & subs, Rowlands & subs, Weidenbach & subs, Hanna & subs, Hill & subs, Phillips & subs; Protocol M/1140/0001 Weidenbach & subs, Protocol M/1140/0045 Segeall & sub, Gainer & subs, Protocol M/1140/0046 Kamitsuka & sub, Protocol M/1140/0048 Stein & Part 7 Labeling for Protocol M/1140/0050

2-5-91 A#85 Submitted Safety Report of pseudomembranous colitis

2-11-91 A#86 Submitted Part 6/1-11 Protocol M/1140/0048 North, 6/12-26 Stevens, 6/27-31 Protocol M/1140/0050 Collins, 6/32-36 Guerra, 6/37-44 Grambau, 6/45-51 Heatley, 6/52-57 Henkle, 6/58-64 VanHook, 6/65 Change in Protocol M1140/0046 Butler, adds sub Platt to Gipson Protocol M/1140/0002

2-7-91 A#86 Addendum to 7-20-90 to include TR 7215/90/015 Pages 1-636

2-18-91 A#87 Submitted Clinical TR's: 1-40 7214/90/008; 41-60 7256/91-003; 61-85 9155/90/002; 86-139 9155/90/022; 140-183 9155/90/034; 184-287 9155/91/028

3-11-91 A#88 Submitted Clinical TR's: Part 6/1-56, 7214-90-052; 6/57-90, 7215-91-004; 6/91-126, 7256-90-003; 6/127-175, 7256-91-003; 6/176-233, 9155-90-020; 6/234-292, 9155-90-025; 6/293-415, 9155-90-029; 6/416-520, 9155-90-030; 6/521-603, 9155-90-031; 6/604-662, 9155-91-002; Chemistry TR's Part 7/663-698, 7254-90-077; 7/699-706, 7256-89-093; 7/707-721, 7256-90-064; 7/722-739, 7256-90-082; 7/740-763, 7256-91-002; Microgiology TR's Part 7/764-780, 7254-90-064; 7/781-795, 7254-90-078; 7/796-810, 7254-90-074; 7/811-822, 7254-90-075; 7/823-852, 7254-90-076; 7/853-866, 7254-90-079; 7/867-888, 7254-90-080; 7/889-910, 7254-90-081; 7/911-924, 7254-90-082; 7/925-940, 7254-90-083; 7/941-978, 7254-90-084; 7/979-997, 7254-90-085; 7/998-1017, 7254-90-086; 7/1018-1032, 7254-90-087; 7/1033-1039, 7254-90-088; 7/1040-1048, 7254-90-089; 7/1049-1074, 7254-90-090; 7/1075-1098, 7254-90-091; 7/1099-1122, 7254-90-093; 7/1123-1188, 7254-90-094; 7/1189-1202, 7254-90-100

3-18-91 A#89 Submitted Part 6 1-17 Protocol M1140/0001 Butler, 6/18-21 Protocol M/1140/0046 Munoz, Part 6/22-46 Protocol M1140/0048 Norman, 6/47-67 Warren, Part 68-93 Protocol M1140/0050 Chodosh, 6/94-108 Green, 6/109-112 Flatt, 6/113 Change in Protocol M/1140/0050 - addition of numerous sub investigators

5-22-91 A#90 Submitted Part 6 Protocol M/1140/0046 Powell 6/1-6, Protocol M/1140/0050 Chiulli 6/7-12, & Michael S. Bronze 6/13-20

5-28-91 Declare the trade name DOXEF to be unacceptable because of safety issues and another name should be proposed

6-1-91 A#91 Submitted Protocol M/1140/0045 Mechenbier 6/1-4, new subs for 0045 & 0046, M/1140/0050 6/5-12 Allen

7-12-91 A#92 Part 6 Protocol M/1140/0046 Kwa 1-5, Green 6-20, Guerra replaces Moreno & subs

7-25-91 A#93 Submitted Part 6/ 1-18 Protocol M/1140/0050 Butler, 6/19-24 Amacher & subs, 6/25-30 Zuschke & subs, 6/31-34 Moskow & subs

8-15-91 A#94 Submitted Part 6 New Investigators for Protocol M/1140/004, 6/1-5 Phillips, 6/6-9 McLean, 6/10-14 Stevens, 6/15-18 Knight, 6/19-22 Arthur, 6/23-26 Snyder, 6/27-30 Duke, 6/31-34 Owings, 6/35-38 Mosley, 39-42 Smith Sr., also adds subs to Marmorstein in Protocol M/1140/0050

8-16-91 A#95 Part 6/1-15 Protocol P/1140/0026, Peters & sub, Part 7/19-20 Labeling

8-30-91 A#96 Submitted new investigator to Protocol M/1140/0050 Powell 1-6

9-27-91 A#97 Submitted ten Safety Reports which represent cases of colitis

10-25-91 A#98 Submitted Part 6/1-5 Protocol M/1140/0045, Matlock

10-30-91 A#99 Submitted Part 6/1-51 Protocol M/1140/0055, 6/52-60 Turner & 3 subs, Part 7/61-68 Labeling

11-11-91 A#100 Submitted Part 7/1-35 Chemistry/ Mfg/Control

11-18-91 A#101 Submitted new investigator to Protocol M/1140/0048, M/1140/0050, Added Sub-Investigator to Protocol M/1140/0050, and new investigator to M/1140/0046

11-26-91 A#102 Submitted Amendment A to Protocol M/1140/0055 "Evaluation of the Hospital Admission Decision in patients with Community-Acquired Pneumonia" with attachment of a list of investigators who were sent Amendment A.

11-26-91 A#102 Stamped receipt

12-2-91 A#102 Submitted protocol amendment, new investigators (M/1140/0045) Bushnell, McLean, Murphy, Woehler, Paugh & Tucker - New investigator (M/1140/0046 Stevens, Tucker - M/1140/0048) Bryant, Adams, Hudson - New investigators (M/1140/0055) Melnick, Rosenthal, Snyder, Bittner, Preheim, Gorby, Dworzack, Horowitz, Safranc, Schroeder, Boken, Lentino, Kirmani, Pachucki, Hecht, Pelletier, Bronze, Mainardi, Lomas, Dretler, Holloway, Maslow, Borkowitz, Barry, Martinez

12-10-91 A#103 - This letter corrects the cover letter for our 12/2/91 submission which was inadvertently assigned Amendment NO. 102

12-13-91 A#104 Submitted new protocol, P/1140/0057 pages 1 - 13, inv Richard J. Davis and part 7 - chemistry/mfg/control information - labeling

12-31-91 A#105 Submitted Annual Report - This report covers the time period from May 1, 1990 - May 1 - 1991.

1-3-91 A#106 Submitted protocol amendment - relocation of inv M/1140/0008 Dr. Barry Carter, added sub/inv and new investigators M/1140/0054 - Susan Andrew, Ralph Ascher, Marc Lebovits, Anthony Krausen, Robert Ciralsky, Joseph Graboyes, Robert Fiddes, Frederick Harcourt, Paul Jacobsen, Thomas Hansbrough, John Matlock, James Atkins, Jean Murphree, Eugenio Chinea, - New investigator M/1140/0054 William Rodriques, Wahood Khan, Om Chhabra, Tahir Sait, Arthur Guarinello, and Alan Smith

1-21-92 A#107 Submitted New Protocol Amendement P/1140/0040

2-10-91 A#108 Submitted M/1140/0045 New Investigator, Terrance C. Kurtz, Co/Inv W. Hadley, Hoyt III, Submitted M/1140/0046 New Investigator Ambriah K. Gupta, Co/Inv Arvind K. Gupta, Submitted M/1140/0046 New Investigator Henry Snead, Co/Inv Justin Ban, Marie Mitchell, Dennis Zachary, John Heffernan, Charles Korte, James Brown, Tim Wochl, Julie Van Beek, Chris White, Submitted M/1140/0048 New Investigator William G. Moseley, Co/Inv D. Howard Lowe, Marianne G. Rochester, Submitted M/1140/0048 New Investigator Thompson H. Southwell, Co/Inv Dewey R. Heetderks. Barnett, Philip T. Hoekstra, Richard J. Kahnoski, Submitted M/1140/0055 New Investigator R. Brooks Gainer, Co/Inv Charlene F. Horan, Norval L. Rasmussen, Edward T. Blume, Robert Curtis and Timothy Nelms. Submitted Amendment A to Protocol M/1140/0055, an optional addition to the protocol for the attending physician to analyse reasons for hospitalization.

3-6-92 A#109 - New investigator to previously submitted protocol M/1140/0048, James E. Clark, MD with sub/inv. George L. Stark, MD. Also addition of sub/inv. to previously submitted protocol M/1140/0048 for Dr. Dean Norman's study, Mira Cantrell, MD and Andrew S. Chan, MD. and addition of sub/inv added to Donald S. North's study, protocol M/1140/0048, John J. Redington, MD. Change in Protocol M/1140/0055, provides an opportunity to analyze the reasons for hospitalization by the attending physician. New investigators to a previously submitted protocol, Dr. Leonard Berkowits replaces Dr. Melanie Maslow as principal investigator with sub/inv Steven Barry, MD and Homer Martiner, Md. Also investigator David M. Parenti, MD with sub/inv. Gary L. Simon, MD and Carmelita U. Tuazon, MD. Addition of sub/inv. to a previously submitted protocol M/1140/0055 Hieu T. Nguyen, MD.

5-18-92 A#110 - Amending the IND to include the following information Clinical (TR 7215/91/025, TR 7215/91/015, TR 7254/90/100, TR 9155/91/005, TR 9155/91/004, TR 9155/90/099)

7-27-92 A# 111 - Submitted new investigator & change in Protocol (M/1140/0055) - new investigator to a previously submitted protocol M/1140/0055, Christopher J. Sullivan, M.D. and subinvestigator, Keith Henry, M.D., Kent Crossley, M.D. Amendment A, protocol M/1140/0055, is an optional addition to the protocol. It provides an opportunity to analyze the reasons for hospitalization by the attending physician.

8-21-92 A# 112 - Submitted new protocol M/1140/0062, "Comparison of Oral Cefpodoxime Proxetil (VANTIN® Tablets) vs Cefaclor (Ceclor®) in the Treatment of Lower Respiratory Tract Infections". New investigator Avinash Patwardhan, M.D. Submitted new labeling.

9-3-92 A# 113 - Submitted Information Amendment Clinical (TR 7215-92-017) "The Effect of Food on Absorption of Cefpodoxime Proxetil Tablets after a 400-mg Dose (Protocol P/1140/0026).

9-8-92 A#114 - Submitted Information Amendment - Part 7 - Chemistry/Mfg/Control, updated stability data

9-14-92 A#115 - Submitted Protocool Amendment, new protocol - M/1140/0063 with new investigator David a. McKinsey, MD. Submitted labeling to Protocol M/1140/0063

9-29-92 A#116 - Submitted Annual Report. This report covers the time period from May 2, 1991 - May 1, 1992.

10-19-92 A#115 Addendum - Cover letter of dated 9-14-92 inadvertantly listed David S. McKinsey, MD, as the primary investigator for Protocol M/1140/00633. The primary investigator for the study is David L. Smith, MD.

10-23-92 A#117 - Added subinvestigators to Dr. Marvin J. Bittner's study, Protocol M/11140/0055: Edward A. Dominquez, MD, Andrea M. Prevan, MD, Mark E. Rupp, MD. Added subinvestigator to Dr. Joseph R. Lentino's study: Vijay V. Yeldandi, MD. Added new investigator to a previously submitted protocol M/1140/0055: Bruce S. Ribner, MD and subinvestigator: India J. Burton, MD. Added new investigator to a previously submitted protocol M/1140/0063: Joseph S. Bertino, Jr., Pharm D and subinvestigators: Anne N. Nafziger, MD,MHS Michael Foltzer, MD, Caterine Puleo, Rn, Linda Stragand, BSN, BS

11-6-92 - Submitted Protocol Amendment, New Investiigator to a previously submitted protocol M/1140/0048 1/3/91 - DDan Osterweil, MD with subinvestigators: Carmen Lamp, Pharm. D. and Loretta Mazorra, RNC, MN,GNP. New Investigator to previously submitted protocol M/1140/0063 on 9/14/92 - John V Temte, MD, PhD with subinvestigator: John Phylis, RPh. New Investigator: Melanie J. Maslow, MD with subinvestigator Waref Azmeh, MD and Adriana Vasquez, MD. New Investigator to previously submitted Protocol M/1140/0055 on 10/30/91 - John F Toney, MD and subinvestigator Douglas Holt, MD and John Groene, MD

APPENDIX C-2

Summary of Correspondence During IND for VANTIN Granules (Formerly called DOXEF Granules)

4-30-92 - A#4 - As a result of a scale-up of this product to production size equipment, it was decided that minor revisions should be made in Item 3. Production lot size, adjustment in the excipient ranges for the amount of Opadry applied, change in order of mixing binder solution components, identification debossed on tablet, removal of in-process control test for film coated tablet moisture.

5-28-92 A#5 - Submitted updated stability data for VANTIN Tablets. Current data on 18 months at room temperature and ambient room temperature, and 12 months at accelerated conditions support a 24 month expiration dating for product packaged in the container-closure systems described in the NDA.

6-2-92 - We are in receipt of the FDA May 7, 1992 review of the Environmental Assessments for VANTIN® Tablets, NDA 50-674 and VANTIN® for Oral Suspension, NDA 50-675. We have listed the FDA comments with our response. This information responds to all deficiencies listed in the May 7 review.

6-9-92 - Provided the following information in response to requests made from June 5, 1992 telephone discussion with Jeff Mehring, Upjohn: 1) Calculations pertaining to environmental concentrations of released substances are shown in Section 8. This includes a calculation for the MEEC. 2) An additonal summary table for environmental parameters.

6-15-92 - Submitted revisions in the package insert doc VANTIN Tablets and Oral Suspension as requested in the FDA review dated March 23, 1992.
6-17-92 - acknowledged receipt

6-16-92 - Notified FDA we had misnumbered two amendments, Amendment No. 4 dated 4-30-92 should be No. 5 & Amendment No. 5 dated 5-28-92 should be No. 6
6-17-92 - acknowledged receipt

6-23-92 - Submitted inserts for distribution in countries other than the United States per FDA request

6-23-92 - Letter to Jerry Abramson, Ph.D., FDA - reference to Item #1 Sankyo has not been assigned a DMF number by the FDA

6-30-92 - Submitted a copy of the cefpodoxime proxetil Environmental Assessment which may be released under Freedom of Information. This fulfills the commitment made in our letter dated June 2, 1992.
7-01-92 - FDA ack'd receipt

7-2-92 - Resubmitted a copy of the cefpodoxime proxetil Environmental Assessment which may be released under Freedom of Information. MSDSs in Item 15 have been replaced with itemized charts.

12-19-91 Submitted revised Microbiology Section in package insert as FDA suggested in fax of 8-14-91 except for retaining "(including penicillinase- and non-penicillianse producing strains)"

1-15-92 Submitted safety update report (see 2 separate volumes)
1-15-92 FDA acknowledged receipt

1-30-91 Submitted draft CFR monographs

2-10-92 - Per telephone discussion of last week, we set the TosoHaas column (Number 8TIM4987 for validation of T/A 1675

2-12-92 A#3 - Submitted completed environmental assessment
2-13-92 Ack'd receipt

3-2-92 - Response to fax dated 2/21/92 we supplied the following information: Solubility/pH profile for cefpodoxime proxetil, and Assay validation and UV spectrum for cefpodoxime proxetil in dissolution medium.

3-10-92 - Provided responses to the deficiencies in the Control/Manufacturing section of the NDA

3-12-92 - A#4 - Submitted technical Report #7215-92-006 entitled Bioequivalence Study of a Clinical Lot and a Production Lot of Cefpodoxime Proxetil Tablets (Protocol P/1140/0040)

3-25-92 - Addendum to A#3, per request of Dr. Phillip Vincent all raw data is submitted in 7 volumes. Only one archival copy will be submitted to each NDA per telephone conversation with Ms Peter Dionne

3-31-92 - We are revising the Microbiology section of the cefpodoxime proxetil tablets and oral suspension insert to include the following statement in the second sentence of the first paragraph: "Cefpodoxime is highly stable in the presence of beta-lactamase enzymes. As a result, many organisms resistant to penicillins and some cephalosporins, due to the presence of beta-lactamases, may be susceptible to cefpodoxime.

4-8-92 - Submitted CMC section of Item 3 "Chemistry-Manufacturing-Control"

4-16-92 - Provided responses to telephone request of 3-26-92

Cefpodoxime Proxetil Tablets (DOXEF®) NDA 50-674 (Name changed to VANTIN® 4-27-92)

3-29-91 Submitted original NDA
3-29-91 FDA acknowledged receipt
5-3-91 Ack. assigns number and states filing date will be 6-2-91
8-13-91 Received fax of the deficiencies in the CMC sections
8-15-91 Received a copy of the Microbiology Section review
3-6-92 extension of FDA review time to 6/29/92
8-7-92 NDA 50-674 and 50-675 are approved effective as of the date of this letter

4-16-91 Notifies FDA that we will deliver equipment to review the Chemistry-Manufacturing-Control sections on 4-18-91 (optical drive, etc.)

5-14-91 Submitted samples for assay methods validation per request of FDA

5-20-91 Submitted corrected pages for TR 9156/91/005
5-21-91 Ack'd receipt

5-29-91 Submitted components and values of the work station delivered to Dr. Susan Alpert on 5-2-91

7-11-91 Lists TUC personnel and issues for discussion for 7-17-91 meeting
7-11-91 Ack'd receipt

7-26-91 Submitted 5 protocols prior to baginning the testing program per meeting of 7-17-91
7-30-91 Ack'd receipt
8-29-91 FDA will accept release of bulk on basis of Sankyo assay. TUC must perform all tests on first 3 lots and every 10th lot thereafter

9-20-91 Submitted A#1 Safety update, 8.1-1.10 including revised integrated Summary of Safety and appropriate tables (Mary still has this submission)
10-1-91 Consider a major amendment and have determined that 180 additional days will be required for its review. New date is 3-14-92

10-4-91 We are providing two copies of domestic pivotal study protocols and lists of investigators per request (2 volumes)

11-11-91 Submitted Environmental Assessment information prepared for inclusion in Sankyo DMF

8-17-92 - Letter to FDA from Kathleen J. Day enclosing press kit for VANTIN® Oral Suspension and Tablets. A copy of final labeling is also provided.
8-31-92 - FDA recommends eliminating use of "extended spectrum" or any comparable claim.

8-19-92 - Letter to FDA from Kathleen J. Day enclosing core introductory promotional matierials for VANTIN® Oral Suspension and Tablets to be used at market launch in October 1992.
9-17-92 - FDA comments and/or recommendations on Primmary Care Introductory Ad and Comprehensive Detailer

9-3-92 - Sent under separate ccover five volumes of data to Marie Bouton, PhD, Roussel UCLAF, Inc. Paris, France which were submitted to the FDA on August 11, 1992.

9-4-92 - Letter to Tatsuo Haneishi, PhD, Deputy Director of Sankyo Company, Ltd informing of the five volume supplement to the VANTIN Tablets New Drug Application.

9-10-92 - Submitted missinig pages 350-378 from Volume 1 of Supplement S-0001, use in bronchitis.

9-17-92 - Letter to FDA stating that we have been informed by Sankyo, Co., Ltd., Tokyo, Japan, that Amendment No. 5 was submitted to their Drug Master File (no number assigned) on August 28, 1992.

9-29-92 - Per request on the August 7, 1992 approval letter we are supplying the FDA one bottle and carton for VANTIN Tablets 100mg and VANTIN for Oral Suspension 100 mg/5 ml.

9-30-92 - Submitted USX7703.00 Value Added Folder (refer to submission of 9/23/92 on Form 2253 for NDA 18-766 for ANSAID® Tablets), USX6399.00 - Borin Reprint, USX6401.00 Dumont Reprint, USX758C.00 Trial Program Enrollment Form, USX6947.00 Indications and Dosage Guide and package insert code 5R2105/1

10-6-92 - Letter from Kathleen J. Day to FDA sending the final revised copy of the introductory multi-disease presenter for VANTIN® Oral Suspension and Tablets, USX6406.00.

10-6-92 - Letter from Kathleen J. Day to FDA sending final revised copies of introductory promotional materials for VANTIN® Oral Suspension and Tablets.

10-13-92 - Letter to Dr. Lumpkin, MD, TUC is aware that the data with Dr. Susan Alpert plans to use in her presentation of the CANDAR to the Pharmaceutical Manuufacturers Association is releasable under Freedom of Information.

11-6-92 - Expedited Review, Submitted a revised package insert for VANTIN® Tablets and Oral Suspension to delete agranulocytosis and pancytopenia as Laboratoory Chhanges occurring in pediatric patients.
11-12-92 - FDA acknowledged receipt of 11-9-92, supplement number S-002

11-13-92 - Submitted Brochures USX6393.00, USX6437.00, USX6406.00, USX7661.00, File Cards USX6394.00, Price List USX6413.00, Promotional Letters USD6414.00, USD6416.00, USD6415.00, Literature Reprint USX6402.00, USX7785.00, Other Materials USX7350.00, USX7489.00, USD7800.00 and Package Insert 5R2105/1

11-25-92 - Submitted Brochures USX6395.00, USX7349.00 and USX6397.00, Promotional letters USD7577.00, USD7698.00, USD7700.00, USD7581.00, USD7699.00, USD7871.00 and other materials USD6408.00 and USX7578.00 and package insert 5R 2105-1

APPENDIX C-3

Summary of Correspondence During NDA for VANTIN Tablets (Formerly called DOXEF Tablets)

	IND	ANUM	PART	SDATE	PAT_TRNUM	RPAGE
1	0000033641	0	TD	9/ 6/89	N/A	3/279
2		0	NS	9/ 6/89		1/199
3		0	NS	9/ 6/89		1/263
4		0	NS	9/ 6/89		1/304
5		0	MD	9/ 6/89		2/7
6		0	MD	9/ 6/89		2/6
7		0	MD	9/ 6/89		2/5
8		0	MD	9/ 6/89		2/4
9		0	MD	9/ 6/89		2/3
10		0	MD	9/ 6/89		2/27
11		0	MD	9/ 6/89		1/344
12		0	NS	9/ 6/89		1/380
13		0	NS	9/ 6/89		3/84 - 3/106
14		0	TD	9/ 6/89	7227/89/071	3/3
15		0	TD	9/ 6/89	N/A	3/276
16		0	TD	9/ 6/89	N/A	3/268 - 275
17		0	TD	9/ 6/89	7227/89/085	
18						
19						
20						
21						
22						
23						
24						

	COMN
1	SUMMARY OF PEDIATRIC STYS CONDUCTED BY SANKYO CO LTD W/CEFPODOXIME PROXETIL# #
2	SEE M/1140/0013 "COMP OF CEFPOD PROX OS (100MG/5ML)VS AMOXICILLIN/CLAVULANATE #POT OS (250MG/5ML) IN TRTMNT OF ACUT
3	E SUPPURATIVE OTITIS MEDIA IN INFANTS & CH#ILDREN" PGS 1/163
4	SEE M/1140/0014 "COMP OF CEFPOD PROX OS(100MG/5ML)VS AMOXICILLIN/CLAVULANATE P#OT OS (250MG/5ML) IN TRTMNT OF ACUTE
5	SUPP OTITIS MEDIA IN INFANTS & CHILDREN" #PGS 1/227C
6	SEE M/1140/0020"COMP OF CEFPOD PROX OS(100MG/5ML) VS TRIMETHOPRIM/SULFAMETHOXA#ZOLE OS (40MG TRIMETH & 200MG SULFAM
7	/5ML)IN TRTMNT OF UNCOMP URIN TRACT INFECT# IN INFANTS & CHILDREN" PG 1/266 OF THIS SUB
8	CONTROL TEST/ASSAY PROCEDURE T/ABRD29# #
9	REGIS SPECS EDP NO. R260# #
10	SPECS & ASSAY METHODS# #
11	METHOD OF MANUFACTURE# #
12	Q/Q FORMULA# #
13	SPECS FOR INACTIVE INGREDIENTS# #
14	SEE M/1140/0027 "COMP OF CEFPOD PROX OS(100MG/5ML) & PENICILLIN V OS(250MG/5ML#) IN TRTMNT OF ACUTE STREP PHARYNGIT
15	IS/TONSILLITIS IN INFANTS & CHILDREN" PG 1#/310
16	SEE M/1140/0028 "COMP OF CEFPOD PROX OS (100MG/5ML)&PENICILLIN V POTASS OS (25#0MG/5ML) IN TRTMNT OFF ACUTE STREPTOC
17	OCCAL PHARYN/TONSILLITISI N INFANTS & CHIL#DREN" PG 1/349
18	"U76252: ACUTE TOX STY OF CS807 IN INFANT RATS (NISTARIMANICHI) W/ORAL ADMIN" #RC PIPER, TF PLATTE 5/22/89#
19	DRUG SAFETY REPORT# #
20	LOCATION OF ALL TOX STYS CONDUCTED BY SANKYO ARE ON FILE AT SANKYO TOKYO, JAPA#N. FINAL REPS CONDUCTED BY TOC ARE O
21	N FILE AT 301 HENREITTA ST#
22	"U76253A: SUBCHRONIC SUBCUTANEOUS STY TO EVALUATE POSSIBLE EFFECTS ON MALE REP#RODUCTIVE SYSTEM OF NEONATAL RATS" R
23	C PIPER, TF PLATTE 6/7/89#
24	

	IND	ANUM	PART	SDATE	PAT_TRNUM	RPAGE
26	0000033641	0	TD	9/ 6/89	7227/89/078	3/189 - 3/267
27		0	TD	9/ 6/89	7227/89/072	3/117 - 3/187
28		0	TD	9/ 6/89	7227/89/084	3/111 - 3/116
29		0	TD	9/ 6/89	N/A	3/1
30		0	MD	9/ 6/89		2/2
31		0	MD	9/ 6/89		2/17
32		0	MD	9/ 6/89		2/15
33		0	CD	9/ 6/89	N/A	2/1
34		0	BD	9/ 6/89	N/A	2/43
35		1	NS	10/24/89		209
36		1	NS	10/24/89		206
37		1	NS	10/24/89		205
38		1	NS	10/24/89		184
39		1	NS	10/24/89		180
40		1	NS	10/24/89		175
41						
42						
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	COMM
26	"U76252: 1 MONTH ORAL TOXS STY IN INFANT DOGS (SUPPLEMENTAL STY AT LOWER DOSES#) RC PIPER, TF PLATTE 5/25/89#
27	"U76252 1 MONTH ORAL TOX STY IN INFANT DOGS" RC PIPER TF PLATTE 5/25/89# #
28	"U76252 4WK ORAL TOX STUDY IN INFANT WISTARIMAMICHI RATS" RC PIPER, TF PLATTE #6/7/89#
29	ALL PHARM REPS FOR CEFPOD PROX HAVEW BEEN PREV SUB TO IND 30254 PCT-# #
30	THIS PAGE ALSO CONTAINS: METHOD OF MANUF, SPECIFICATIONS & ASSAY, IMPURITIES, #REFERENCE STANDARD, BATCH ANALYSIS,
31	BULK DRUG STAB DATA#
32	LIST OF COMPOUNDS & THEIR APPROX RETENTION TIME# #
33	DESC OF ASSAY; SPECIFICITY; LINEARITY & RECOVERY; PRECISION; ASSAY REGGUDNESS;# PLACEBO SAMPLE CHROMATOGRAPHY; CHRO
34	MATOGRAMS#
35	DRUG SUBSTANCE: DESC & STRUCTURE, PHYSICAL & CHEMICAL CHARACTERISTICS# #
36	ENVIRONMENTAL ANALYSIS IS ATTACHED (ASSESSMENT STATEMENT)# #
37	SEE M/1140/0027 "COMP OF CEFPOD PROX O SUSP(100MG/5ML) & PENICILLIN VS POTASSI#UM O SUSP(250MG/5ML) IN TRTMNT OF AC
38	UTE STREPTOCOCCAL PHARYNGITIS/TONSILLITIS #IN INFANTS & CHILDREN" SUB 9/6/89 ORIG SUB PG 1/310
39	SEE M/1140/0027 "COMP OF CEFPOD PROX O SUSP(100MG/5ML) & PENICILLIN VS POTASSI#UM O SUSP(250MG/5ML) IN TRTMNT OF AC
40	UTE STREPTOCOCCAL PHARNGITIS/TONSILLITIS J#IN INFANTS & CHILDREN" SUB 9/6/89 ORIG SUB PG 1/310
41	SEE M/1140/0027 "COMP OF CEFPOD PROX O SUSP(100MG/5ML) & PENICILLIN VS POTASS#IUM O SUSP(250MG/5ML) IN TRTMNT OF A
42	CUTE STREPTOCOCCAL PHARYNGITIS/TONSILLITIS# IN INFANTS & CHILDREN" SUB 9/6/89 ORG SUB PG 1/310
43	SEE M/1140/0027 "COMP OF CEFPOD PROX O SUSP(100MG/5ML) & PENCILLIN VS POTASSIU#M S SUP(250MG/5ML) IN TRTMNT OF ACUT
44	E STREPTOCOCCAL PHARYNGITIS/TONSILLITIS IN# INFANTS & CHILDREN" SUB 9/6/89 ORIG SUB PG 1/310
45	SEE M/1140/0027 "COMP OF CEFPOD PROX O SUSP(100MG/5ML) & PENICILLIN VS POTASSI#UM O SUSP(250MG/5ML) IN TRTMTT OF A
46	CUTE STREPTOCOCCAL PHARYNGITIS/TONSILLITIS# IN INFANTS & CHILDREN" SUB 9/6/89 ORIG SUB PG 1/310
47	SEE M/1140/0027 "COMP OF CEFPOD PROX O SUSP(100MG/5ML) & PENICILLIN VS POTASSI#UM O SUSP(250MG/5ML) IN TRTMNT OF AC
48	UTE STREPTOCOCCAL PHARYNGITIS/TONSILLITIS #IN INFANTS & CHILDREN" SUB 9/6/89 ORIG SUB PG 1/310
49	

	IND	ANUM	PART	SDATE	PAT_TRNUM	RPAGE
51	0000033641	1	NS	10/24/89		169
52		1	NS	10/24/89		168
53		1	NS	10/24/89		167
54		1	NS	10/24/89		145
55		1	NS	10/24/89		140
56		1	NS	10/24/89		139
57		1	NS	10/24/89		134
58		1	NS	10/24/89		216
59		1	NS	10/24/89		217
60		1	NS	10/24/89		78
61		1	NS	10/24/89		69
62						
63						

	COMM
51	SEE M/1140/0027 "COMP OF CEFPOD PROX O SUSP(100MG/5ML) & PENICILLIN VS POT O S#USP(250MG/5ML) IN TRTMNT OF ACUTE ST
52	REPTOCOCCAL PHARYNGITIS/TONSILLITIS IN IN#FANTS & CHILDREN" SUB 9/6/89 ORIGI SUB PG 1/310
53	SEE M/1140/0027 "COMP OF CEFPOD PROX O SUSP(100MG/5ML) & PENICILLIN VS POTASSI#UM O SUSP (250MG/5ML) IN TRTMNT OF A
54	CUTE STREPTOCOCCAL PHARYNG/TONSILLITIS IN #INFANTS & CHILDREN" SUB 9/6/89 ORIG SUB PGS 1/310
55	SEE M/1140/0027 "COMP OF CEFPOD PROX O SUSP(100MG/5ML) & PENICILLIN VS POTASS #O SUSP(250MG/5ML) IN TRTMNT OF ACUTE
56	STREP PHARYNGITIS/TONSILLITS IN INFANTS &# CHILDREN" SUB 9/6/89 ORIG SUB PG 1/310
57	SEE M/1140/0020 "COMP OF CEFPOD PROX O SUSP(100MG/5ML) VS TRIMETHOPRIM/SULFAME#THOXAZOLE O SUSP IN THE TRTMNT OF UN
58	COMP URINARY TRACT INFECTS IN INFANTS & CH#ILDREN" SUB 9/6/89 ORIG SUB PG 1/266
59	SEE M/1140/0020 "COMP OF CEFPOD PROX O SUSP(100MG/5ML) VS TRIMETHOPRIM/SULFAME#THOXAZOLE O SUSP IN TRTMNT OF UNCOMP
60	URINARY TRACT INFECTS IN INFANTS & CHILDR#E" SUB 9/6/89 ORIG SUB PGS 1/266
61	SEE M/1140/0020 "COMP OF CEFPOD PROX O SUSP(100MG/5ML) VS TRIMETHOPRIM/SULFAME#THOXAZOLE O SUSP IN TRTMNT OF UNCOMP
62	URINARY TRACT INFECTS IN INFANTS & CHILDR#EN" SUB 9/6/89 ORIG SUB PG 1/266
63	SEE M/1140/0020 "COMP OF CEFPOD PROX O SUSP(100MG/5ML) VS TRIMETHOPRIM/SULFAME#THOXAZOLE O SUSP IN TRTMNT OF UNCOMP
64	URINARY TRACT INFET IN INFANTS & CHILDREN#" SUB 9/6/89 ORIG SUB PG 1/266
65	SEE M/1140/0028 "COMP OF CEFPOD PROS O SUSP(100MG/5ML) & PENICILLIN VS POTASSI#UM O SUSP(250MG/5ML) IN TRTMNT OF AC
66	UTE STREPTOCOCCAL PHARYNGITS/TONSILLITIS I#N INFANTS & CHILDREN" SUB 9/6/89 ORIG SUB PG 1/319
67	SEE M/1140/0028 "COMP OF CEFPOD PROX O SUSP(100MG/5ML) & PENICILLIN VS POTASSI#UM O SUSP(250MG/5ML) IN TRTMNT OF AC
68	UTE STREPTOCOCCAL PHARYNGITIS/TONSILLITIS #IN INFANTS & CHILDREN" SUB 9/6/89 ORIG SUB PG 1/319
69	SEE M/1140/0020 "COMP OF CEFPOD PROX O SUSP(100MG/5ML) VS TRIMETHOPRIM/SULFAME#THOXAZOLE O SUSP IN TRTMNT OF UNCOMP
70	URINARY TRACT INFECTS IN INFANTS & CHILDR#EN" SUB 9/6/89 ORIG SUB PG 1/266
71	SEE M/1140/0020 "COMP OF CEFPOD PROX O SUSP(100MG/5ML) VS TRIMETHOPRIN/SULFAME#THOXAZOLE O SUSP IN TRTMNT OF UNCOMP
72	URINARY TRACT INFECTS IN INFANTS & CHILDR#EN" SUB 9/6/89 ORIG SUB PG 1/266
73	

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75	0000033641	1	NS	10/24/89		63
76		1	NS	10/24/89		59
77		1	NS	10/24/89		54
78		1	NS	10/24/89		48
79		1	NS	10/24/89		39
80		1	NS	10/24/89		271
81		1	NS	10/24/89		269
82		1	NS	10/24/89		265
83		1	NS	10/24/89		260
84		1	NS	10/24/89		257
85		1	NS	10/24/89		251
86						
87						

	CONN
75	SEE M/1140/0020 "COMP OF CEFPOD PROX O SUSP(100MG/5ML) VS TRIMETHOPRIM O SUSP #IN TRTMNT OF UNCOMP URIN TRACT INFZC
76	TS IN INFANTS & CHILDREN" SUB 9/6/89 ORIG #SUB PG 1/266
77	SEE M/1140/0013 "COMP OF CEFPOD PROX O SUSP(100MG/5ML) VS AMOX/CLAVULANATE POT#T O SUSP (250MG/ML) IN TRTMNT OF ACU
78	TE SUPP OTITIS MEDIA IN INFANTS & CHILDREN#" SUB 9/6/89 PG 1/163
79	SEE M/1140/0013 "COMP OF CEFPOD PROX O SUSP(100MG/5ML) VS AMOX/CLAVULANATE POT# O SUSP (250MG/ML) IN TRTMNT OF ACUT
80	E SUPP OTITIS MEDIA IN INFANTS& CHILDREN" #SUB 9/6/89 PG 1/163
81	SEE M/1140/0013 "COMP OF CEFPOD PROX O SUSP(100MG/5ML)VS AMOX/CLAVULANATE POT #O SUSP(250MG/ML) IN TRTMNT OF ACUTE
82	SUPP OTITIS MEDIA IN INFANTS & CHILDREN" S#UB 9/6/89 PG 1/163
83	SEE M/1140/0013 "COMP OF CEFPOD PROX O SUSP(100MG/5ML) VS AMOX/CLAVULANATE POT# O SUSP(250MG/ML) IN TRMNT OF ACUTE
84	SUPP OTITIS MEDIA IN INFANTS & CHILD" SUB #9/6/89 ORIG SUB PG 1/163
85	SEE M/1140/0028 "COMP OF CEFPOD PROX O SUSP(100MG/5ML) & PENICILLIN VS POTASSI#UM O SUSP(250MG/5ML) IN TRTMNT OF AC
86	UTE STREPTOCOCCAL PHARYNGITIS/TONSILLITIS #IN INFANTS & CHILDREN" SUB 9/6/89 PG 1/319
87	SEE M/1140/0028 "COMP OF CEFPOD PROX O SUSP(100MG/5ML) & PENICILLIN VS POTASSI#UM O SUSP(250MG/5ML) IN TRTMNT OF AC
88	TUE STREPTOCOCCAL PHARYNGITIS/TONSILLITIS #IN INFANTS & CHILDREN" SUB 9/6/89 PG 1/319
89	SEE M/1140/0028 "COMP OF CEFPOD PROX O SUSP(100MG/5ML) & PENICILLIIN VS POTASS#IUM O SUSP(250MG/5ML) IN TRTMNT OF A
90	CUTE STREPTOCOCCAL PHARYNGITIS/TONSILLITIS# IN INFANTS & CHILDREN" SUB 9/6/89 PG 1/319
91	SEE M/1140/0028 "COMP OF CEFPOD PROXX O SSUP(100MG/5ML) & PENICILLIN VS POTASS#IUUM O SUSP(250MG/5ML)IN TRTMNT OF A
92	CUTE STRRPTOCOCCAL PHARYNGITIS/TONSILLITIS# IN INFANTS & CHILD" SUB 9/6/89 PG 1/319
93	SEE M/1140/0028 "COMP OF CEFPOD PROX O SUSP(100MG/5ML) & PENICILLIN VS POTASS#IUM O SUSP(250MG/5ML) IN TRTMNT OF A
94	CUTE STREPTOCOCCAL PHARYNGITIS/TONSILLITIS# IN INFANTS & CHILDREN" SUB 9/6/89 PG 1/319
95	SEE M/1140/0028 "COMP OF CEFPOD PROX O SUSP(100MG/5ML) & PENICILLIN VS POTASSI#UM ORAL SUSP(250MG/5ML) IN TRTMNT OF
96	ACUTE STREPTOCOCCAL PHARYNGITIS/TONSILLIT#IS IN INFANTS & CHILDREN" SUB 9/6/89 ORIG SUB PG 1/319
97	

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99	0000033641	1	NS	10/24/89		12
100		1	NS	10/24/89		115
101		1	NS	10/24/89		1
102		1	NS	10/24/89		85
103		2	NS	11/ 2/89		68
104		2	NS	11/ 2/89		63
105		2	NS	11/ 2/89		61
106		2	NS	11/ 2/89		54
107		2	NS	11/ 2/89		50
108		2	NS	11/ 2/89		39
109		2	NS	11/ 2/89		31
110						
111						
112						
113						
114						
115						
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117						
118						
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120						
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99	SEE M/1140/0013"COMP OF CEFPOD PROX O SUSP(100MG/5ML) VS AMOX/CLAVULANATE POT #O SUSP(250MG/ML) IN TRTMNT OF ACUTE
100	SUPP OTITIS MEDIA IN INFANTS&CHILD" SUB 9/#6/89 ORIG SUB PG 1/163
101	SEE M/1140/0020 "COMP OF CEFPOD PROX O SUSP(100MG/5ML) VS TRIMETHOPRIM/SULFAME#THOXAZOLE O SUSP IN TRTMNT OF UNCOMP
102	URIN TRACT INFECTS IN INFANTS & CHIRDREN"# SUB 9/6/89 ORIG SUB 1/266
103	SEE M/1140/0013 "COMP OF CEFPOD PROX OS(100MG/5ML) VS AMOX/CLAVULANATE POT ORA#L SUSP(250MG/ML) IN TRTMNT OF ACUTE
104	SUPP OTITIS MEDIA IN INFANT & CHILD" SUB 9#/6/89 ORIG SUB PG 1/163
105	SEE M/1140/0020 "COMP OF CEFPOD PROX O SUSP(100MG/5ML) VS TRIMETHOPRIM/SULFAME#THOXAZOLE IN TRTMNT OF UNCOMP URINA
106	RY TRACT INFECTS IN INFANTS & CHILDREN" SU#B 9/6/89 ORIG SUB PG 1/266
107	SEE M/1140/0027"COMP OF CEFPOD PROX OSUSP(100MG/5ML) & PENICILLIN POTASS OSUSP#(250MG/5ML) IN TRTMNT OF ACUTE STREP
108	TOCOCCAL PHARNGITIS/TONSILLITIS IN INFANTS# & CHILDREN" SUB 9/6/89 PG 1/310
109	SEE M/1140/0027"COMP OF CEFPOD PROX OSUSP(100MG/5ML)&PENICILLIN V POTASS OSUSP#(250MG/5ML) IN TRTMNT OF ACTUE STREP
110	TOCOCCAL PHARYNGITIS/TONSILLITIS IN INFANT#S & CHILD" SUB 9/6/89 PG 1/310
111	SEE M/1140/0020"COMP OF CEFPOD PROX OSUSP(100MG/5ML) VS BACTRIM OSUSP(40MG TRI#METHOPRIM&200MGSULFAMETHOXAZOLE/5ML)
112	IN TRTMNT OF UNCOMP URINARY TRACT INFECTS# IN INFANTS & CHILD" SUB 9/6/89 PG 1/266
113	SEE M/1140/0020"COMP OF CEFPOD PROX OSUSP(100MG/5ML) VS BACTRIM OSUSP (40MG TR#IMETH&200MG SULFAMETHOXAZOLE/5ML) IN
114	TRTMNT OF UNCOMP URINARY TRACT INFECTS IN# INFANTS & CHILD" SUB 9/6/89 PG 1/266
115	SEE M/1140/0013 "COMP OF CEFPOD PROX OSUSP(100MG/5ML) VS AUGMENTIN O SUSP(250M#G/ML) IN TRTMNT OF ACUTE SUPP ORITIS
116	MEDIA IN INFANTS & CHILDREN" SUB 9/6/89 P#G 1/163 ORIG SUB
117	SEE M/1140/0013"COMP OF CEFPOD PROX O SUSP(100MG/5ML) VS AUGMENTIN O SUSPO (25#0MG/ML) IN TRTMNT OF ACUTE SUPPURATI
118	VE OTITIS MEDIA IN INFANTS & CHILDREN" SUB# 9/6/89 ORG SUB PG 1/163
119	SEE M/1140/0013 "COMP OF CEFPOD PROX OSUSP(100MG/5ML) VS AUGMENTIN O SUSP(250M#G/ML) IN TRTMNT OF ACUTE SUPP ORITIS
120	MEDIA IN INFANTS & CHILDREN" SUB 9/6/89 P#G 1/163
121	

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123	0000033641	2	NS	11/ 2/89		1
124		3	NS	11/17/89		1
125		3	NS	11/17/89		10
126		3	NS	11/17/89		37
127		3	NS	11/17/89		5
128		3	NS	11/17/89		52
129		3	NS	11/17/89		57
130		3	NS	11/17/89		75
131		3	NS	11/17/89		81
132		3	NS	11/17/89		88
133		4	NS	1/ 9/90		1
134						
135						

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123	SEE M/1140/0013 "COMP OF CEFPOD PROX OSUSP (100MG/5ML) VS AUGMENTIN OSUSP (250#MG/ML) IN TRTMNT OF ACUTE SUPPURATIV
124	E OTITIS MEDIA IN INFANTS & CHILD" SUB 9/6#/89 ORIG SUB PG 1/163
125	SEE M/1140/0013 "COMP OF CEFPOD PROX OSUSP(100MG/5ML) VS AUGMENTIN ORAL SUSP (#250MG/ML) IN TRTMNT OF ACUTE SUPPURA
126	TIVE OTITIS MEDIA IN INFANTS & CHILD" SUB #9/6/89 ORIG SUB PG 1/163
127	SEE M/1140/0013 "COMP OF CEFPOD PROX OSUSP(100MG/5ML) VS AUGMENTIN OSUSP 250MG#/ML IN TRTMNT OF ACUTE SUPP OTITIS M
128	EDIA IN INFANTS & CHILD" SUB 9/6/89 ORIG S#UB PG 1/163
129	SEE M/1140/0020 "COMP OF CEFPOD PROX OSUSP 100MG/5ML VS BACTRIM OSUSP 40MGTRI#METHOPRIM & 200MG SULFAMETHOXAZOLE/5
130	ML IN TRTMNT OF UNCOMP URINARY TRACT INFEC#TS IN INFANTS & CHILD" SUB 9/6/89 ORIG SUB PG 1/266
131	SEE M/1140/0013 "COMP OF CEFPOD PROX OSUSP(100MG/5ML) VS AUGMENTIN OSUSP (250M#G/ML) IN THE TRTMNT OF ACUTE SUPP OT
132	ITIS MEDIA IN INFANTS & CHILD" SUB 9/6/89 #ORIG SUB PG 1/163
133	SEE M/1140/0020 "COMP OF CEFPOD PROX OSUSP 100MG/5ML VS BACTRIM OSUSP 40MG TRI#METHOPRIM & 200MG SULFAMETHOXAZOLE/5
134	ML IN TRTMNT OF UNCOMP URIN TRACT INFECTS #IN INFANTS & CHILD" SUB 9/6/89 ORIG SUB PG 1/266
135	SEE M/1140/0020 "COMP OF CEFPOD PROX OSUSP 100MG/5ML VS BACTRIM SSUSP 40MG TRI#METHOPRIM & 200MG SULFAMETHOXAZOLE/5
136	ML IN TRTMNT OF UNCOMP URINARY TRACT INFEC#TS IN INFANTS & CHILD" SUB 9/6/89 PG 1/266 ORIG SUB
137	SEE M/1140/0027 "COMP OF CEFPOD PROX OSUSP(100MG/5ML) & PENICILLIN V POT OSUSP#(250MG/5ML) IN TRTMNT OF ACUTE STREP
138	TOCOCCAL PHARYNGITIS/TONSILLITIS IN INFANT#S & CHILDREN" SUB 9/6/89 ORIG SUB PG 1/310
139	SEE M/1140/0028 "COMP OF CEFPOD PROX OSUSP(100MG/5ML) & PENICILLIN V POT OSUSP# (250MG/5ML) IN TRTMNT OF ACUTE STRE
140	PTOCOCCAL PHARYNGITIS/TONSILLITIS IN INFAN#TS & CHILD" SUB 9/6/89 ORIG SUB PG 1/319
141	SEE M/1140/0028 "COMP OF CEFPOD PROX OSUSP(100MG/5ML) & PENICILLIN V POT OSUSP# (250MG/5ML) IN TRTMNT OF ACUTE STRE
142	PTOCOCCAL PHARYN/TONSILL IN INFANTS & CHIL#D" SUB 9/6/89 ORIG SUB PG 1/319
143	SEE P/1140/0032 "PHARMACOKINETICS OF CEFPOD IN PEDIATRIC PTS FLLWING ADMIN OF #CEFPOD PROXETIL FOR ORAL SUSP" PGS 2
144	-20 OF THIS SUB#
145	

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147	0000033641	5	NS	1/20/90		9
148		5	NS	1/20/90		1
149		5	NS	1/30/90		82
150		5	NS	1/30/90		78
151		5	NS	1/30/90		77
152		5	NS	1/30/90		75
153		5	NS	1/30/90		59
154		5	NS	1/30/90		25
155		5	NS	1/30/90		41
156		5	NS	1/30/90		46
157		5	NS	1/30/90		50
158						
159						

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147	SEE M/1140/0020 "COMP OF CEFPOD PROX OSUSP(100MG/5ML) VS BACTRIM OSUSP(40MG TR#IMETHOPRIM&200MG SUULFAMETH) IN TRTM
148	NT OF UNCOMP URINARY TRACT INFECTS IN INFA#NTS & CHILD" SUB 9/6/89 PGS 1/266
149	SEE M/1140/0013 "COMP OF CEFPOD PROX OSUSP(100MG/5ML) VS AUGMENTIN OSUSP(250MG#/ML) IN TRTMNT OF ACUTE SUPPURATIVE
150	OTITIS MEDIA IN INFANTS & CHILD" SUB 9/6/8#9 PG 1/163 ORIG SUB
151	SEE M/1140/0028 "COMP OF CEFPOD PROX OSUSP(100MG/5ML) & PENICILLIN V POT OSUSP#(250MG/5ML) IN TRTMNT OF ACUTE STREP
152	PHARYNGITIS/TONSILLITIS IN INFANTS & CHIL#D" SUB 9/6/89 ORIG SUB PG 1/319
153	SEE M/1140/0028 "COMP OF CEFPOD PROX OSUSP(100MG/5ML) & PENICILLIN V POT OSUS#P(250MG/5ML) IN TRTMNT OF ACUTE STRE
154	P PHARNGITIS/TONSILLITIS IN INFANTS & CHIL#D" SUB 9/6/89 ORIG SUB PG 1/319
155	SEE M/1140/0027 "COMP OF CEFPOD PROX OSUSP(100MG/5ML) & PENICILLIN V POT OSUSP#(250MG/5ML) IN TRTMNT OF ACUTE STREP
156	TOC PHARNGITIS/TONSILL IN INFANTS & CHILD"# SUB 9/6/89 ORIG SUB 1/310
157	SEE M/1140/0027 "COMP OF CEFPOD PROX OSUSP(100MG/5ML) & PENICILLIN V POT OSUSP#(250MG/5ML) IN TRTMNT OF ACUTE STREP
158	T PHARNYGITIS/TONSILLITIS IN INFANTS & CHI#LD" SUB 9/6/89 ORIG SUB PG 1/310
159	SEE M/1140/0027"COMP OF CEFPOD PROX OSUSP(100MG/5ML) & PENICILLIN V POT OSUSP(#250MG/5ML) IN TRTMNT OF ACUTE STREPT
160	PHARNG/TONBILL IN INFANTS & CHILD" SUB 9/#6/89 ORIG SUB PG 1/310
161	SEE M/1140/0020 "COMP OF CEFPOD PROX OSUSP(100MG/5ML) VS BACTRIM OSUSP(40MG TR#IMETHOPRIM&200MG SULFAMETH/5ML) IN T
162	RTMNT OF UNCOMP URIN TRACT INFECTS IN INFA#NTS&CHILD" SUBV 9/6/89 ORIG SUB PG 1/266
163	SEE M/1140/0020"COMP OF CEFPOD PROX OSUSP(100MG/5ML) VS BACTRIM OSUSP(40MG TRI#METH&200MG SULFAMETH/5ML) IN TRTMNT
164	OF UNCOMP URIN TRACT INFECTS IN INFANTS & #CHILD" SUB 9/6/89 ORIG SUB PG 1/266
165	SEE M/1140/0020"COMP OF CEFPOD PROX OSUSP(100MG/5ML) VS BACTRIM OSUSP(40MG TRI#METH&200MGSULFAMETH/5ML) IN TRTMNT O
166	F UNCOMP URIN TRACT INFECTS IN INFANTS&CHI#LD" SUB 9/6/89 ORIG SUB PG 1/266
167	SEE M/1140/0027"COMP OF CEFPOD PROX OSUSP(100MG/5ML) & PENICILLIN V POT OSUSP(#250MG/5ML) IN TRTMNT OF ACUTE STREPT
168	OCOCCAL PHARYNG/TONSILL IN INVANTS&CHILD" #SUB 9/6/89 ORIG SUB PG 1/310
169	

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171	0000033641	5	NS	1/30/90		54
172		7	NS	2/20/90		1
173		7	NS	2/20/90		5
174		7	NS	2/20/90		8
175		8	CD	3/ 9/90	7228/90/009	83
176		8	NS	3/ 9/90		1
177		8	NS	3/ 9/90		4
178		8	NS	3/ 9/90		70
179		8	TD	3/ 9/90	7228/89/019	82
180		8	CD	3/ 9/90	7228/89/019	82
181		10	NS	4/ 3/90		1
182						
183						

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171	SEE M/1140/0027 "COMP OF CEFPOD PROX SOSUP(100MG/5ML) & PENICILLIN V POT OSUSP#(250MG/5ML) IN TRTMNT OF ACUTE STREP
172	PHARNG/TONSILL IN INFANTS & CHILD" SUB 9/#6/89 ORIG SUB PG 1/310
173	SEE M/1140/0020 "COMP OF CEFPOD PROX(40MGSUSP 100MG/5ML) VS BACTRIM ORAL SUSP #(40MG TRIMETHOPRIM&200MG SULFAMETHOX
174	AZOLE/5ML) IN TRTMNT OF UNCOM URIN TRACT I#NFECT IN INFANTS&CHILD" SUB 9/6/89 ORIG SUB PG 1/266
175	SEE M/1140/0020 "COMP OF CEFPOD PROX(40MG SUSP 100MG/5ML) VS ACTRIM OSUSP 40MG# SULFAMETHOXAZOLE & 200MG SULFAMETHO
176	XAZOLE/5ML IN TRTMNT OF UNCOMP URIN TRACT #INFECT IN INFANTS&CHILD" SUB 9/6/89 ORIG SUB PG 1/266
177	SEE M/1140/0028 "COMP OF CEFPOD PROX OSUSP(100MG/5ML) AND PENICILLIN V POT OSU#SP(250MG/5ML) IN TRTMNT OF ACUTE STR
178	EPTOCOCCAL PHARYNGITIS/TONSILLITIS IN INFA#NTS & CHILD" SUB 9/6/89 ORIG SUB PG 1/319
179	"U76252: A. SEGMENT I FERTILITY AND GENERAL REPRODUCTIVE PERFORMANCE STUDY (ORAL) IN RAT" ET AL 2/19/90 FOR COMP C
180	OPY OF REP SEE IND-30254 AMD 54 SUB 3/9/90# ABSTRACT ONLY
181	SEE M/1140/0020 "COMP OF CEFPOD PROX OSUSP(100MG/5ML) VS BACTRIM OSUSP(40MG TR#IMETHOPRIM&200MG SULFAMETHOXAZOLE/5M
182	L) IN TRTMNT OF UNCOM URIN TRACT INFECTS I#N INFANTS&CHILD" SUB 9/6/89 PG 1/266
183	SEE M/1140/0020 "COMP OF CEFPOD PROX OSUSP(100MG/5ML) V TRIMETHOPRIM/SULFAMETH#OXAZOLE OSUSP(40MGTRIMETHOP & 200MGS
184	ULFAMETH/5ML) IN TRTMNT OF UNCOMP URINARY #TRACT INFECTS IN INFANTS&CHILD" SUB 9/6/89 PG 1/266
185	SEE M/1140/0020 "COMP OF CEFPOD PROX OSUSP(100MG/5ML) VS BACTRIM OSUSP(40MG TR#IMETHOPRIM&200MG SULFAMETHOXAZOLE/5M
186	L) IN TRTMNT OF UNCOMP URIN TRACT INFECT I#N INFANTS & CHILD" SUB 9/6/89 PG 1/266
187	"EVALUATION OF U76252 IN THE SALMONELLA/MICROSOME TEST (AMES ASSAY)" CS AARON #12/20/89 FOR COMP COPY OF REP SEE IN
188	D-30254 AMD 54 SUB 3/9/90 ABSTRACT ONLY#
189	"EVALUATION OF U76252 IN THE SALMONELLA/MICROSOME TEST (AMES ASSAY)" CS AARON #12/20/89 FOR COMPLETE COPY OF THIS R
190	EP SEE AMD 54 IND-30254 SUB 3/9/90#
191	SEE M/1140/0013 "COMP OF CEFPOD PROX OSUSP(100MG/5ML) VS AUGMENTIN OSUSP(250MG#/5ML) IN TRTMNT OF ACUTE SUPP OTITIS
192	MEDIA IN INFANTS & CHILD" SUB 6/9/89#
193	

	IND	AMUM	PART	SDATE	PAT_TRMUM	RPAGE
195	0000033641	10	NS	4/ 3/90		4
196		10	NS	4/ 3/90		5
197		12	NS	4/23/90		6/0001
198		13	NS	4/30/90		6/2
199		13	NS	4/30/90		6/29
200		13	NS	4/30/90		6/5
201		17	NS	5/31/90		6/10
202		17	NS	5/31/90		6/6
203		19	NS	7/11/90		6/2
204		22	NS	9/25/90		4
205		22	NS	9/25/90		4
206		22	NS	9/25/90		54
207		22	NS	9/25/90		54
208						

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195	SEE M/1140/0020 "COMP OF CEFPOD PROX OSUSP(100MG/5ML) VS BACTRIM OSUSP (40MG T#RIMETHOPRIM &200MG SULFAMETH/5ML) IN
196	TRTMNT OF UNCOMP URINARY TRACT INFECTS IN# INFANTS & CHILD" SUB 9/9/89
197	SEE M/1140/0020 "COMP OF CEFPOD PROX OSUSP(100MG/5ML) VS BACTRIM OSUSP (40MG T#RIMETH &200MG SULFAMETH/5ML) IN TRTM
198	NT OF UNCOMP URINARY TRACT INFECTS IN INFA#NTS & CHILD" SUB 9/9/89
199	M/A# #
200	COMPARISON OF CEFPODOXIME PROXETIL ORAL SUSPENSION VS TRIMETHOPRIM/SULFAMETHOX#AZOLE ORAL SUSPENSION IN THE TREATME
201	NT OF UNCOMPLICATED URINARY TRACT INFECTIO#NS IN INFANTS AND CHILDREN 9/6/89
202	COMPARISON OF CEFPODOXIME PROXETIL ORAL SUSPENSION VS TRIMETHOPRIM/SULFAMETHOX#AZOLE ORAL SUSPENSION IN THE TREATME
203	NT OF UNCOMPLICTED URINARY TRACT INFECTIO#S IN INFANTS AND CHILDREN 9/6/89
204	COMPARISON OF CEFPODOXIME PROXETIL ORAL SUSPENSION VS TRIMETHOPRIM/SULFAMETHOX#AZOLE ORAL SUSPENSION IN THE TREATME
205	NT OF UNCOMPLICATED URINARY TRACT INFECTIO#NS IN INFANTS AND CHILDREN 9/6/89
206	"COMPARISON OF CEFPODOXIME PROXETIL ORAL SUSPENSION VS TRIMETHOPRIM/SULFAMETHO#AZOLE ORAL SUSPENSION IN THE TRSTME
207	NT OF UNCOMPLICATED URINARY TRACT INFECTIO#NS IN INFANTS AND CHILDREN" 9/6/89
208	""COMPARISON OF DOXEF PROXETIL ORAL SUSPENSION VS TRIMETHOPRIM/SULFAMETHOXAZOL#E ORAL SUSPENSION IN THE TREATMENT O
209	F UNCOMPLICATED URINARY TRACT INFECTIONS I#N INFANTS AND CHILDREN" 9/6/89
210	"COMPARISON OF CEFPODOXIME PROXETIL ORAL SUPENSION VS TRIMETHOPRIM/SULFAMETHOX#AZOLE ORAL SUSPENSION IN THE TREATME
211	NT OF UNCOMPLICATED URINARY TRACT INFECTI#ONS IN INFANTS AND CHILDREN" DATED 09/06/89
212	"COMPARISON OF CEFPODOXIME PROXETIL POWDER FOR ORAL SUSPENSION (DOXEF) VS CEFI#XIME POWDER FOR ORAL SUSPENSION (SUP
213	RAX)" 9/25/90#
214	"COMPARISON OF CEFPODOXIME PROXETIL POWDER FOR ORAL SUSPENSION (DOXEF) VS CEFI#XIME POWDER FOR ORAL SUSPENSION (SUP
215	RAX)" 9/25/90#
216	"COMPARATIVE BIOAVAILBILITY OF TWO FORMULATIONS OF CEFPODOXIME PROXETIL FOR OR#AL SUSPENSION" 9/25/90#
217	"COMPARATIVE BIOAVAILABILITY OF TWO FORMULATIONS OF CEFPODOXIME PROXETIL FOR O#RAL SUSPENSION" 9/25/90#
218	

	IND	ANUM	PART	SDATE	PAT TREUM	RPAGE
220	0000033641	22	NS	9/25/90		4
221		23	NS	10/31/90		2
222		23	NS	10/31/90		22
223		23	NS	10/31/90		34
224		23	NS	10/31/90		18
225		23	NS	10/31/90		34
226		25	NS	12/18/90		1
227						
228		25	NS	12/18/90		13
229						
230		25	NS	12/18/90		5
231						
232		26	SD	3/11/91	9155/90/021	54 - 100
233		26	SD	3/11/91	9155/90/021	54 - 100
234		26	SD	3/11/91	9155/90/021	54 - 100
235		26	SD	3/11/91	9155/90/021	54 - 100
236		26	SD	3/11/91	9155/90/021	54 - 100
237		26	SD	3/11/91	9155/90/018	6-53
238						
239		26	SD	3/11/91	9155/90/018	6-53
240		26	SD	3/11/91	9155/90/018	6-53
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220	"COMPARISON OF CEFPODOXIME PROXETIL POWDER FOR ORAL SUSPENSION (DOXEP) VS CEFI#XIME POWDER FOR ORAL SUSPENSION (SUP
221	RAX) " 9/25/90#
222	"COMPARISON OF DOXEF PROXETIL POWDER FOR ORAL SUSPENSION VS CEFIXIME POWDER FO#R ORAL SUSPENSION" 9/25/90#
223	"COMPARISON OF DEXEF PROXETIL POWDER FOR ORAL SUSPENSION VS CEFXIME POWDER" 9#/25/90#
224	"COMPARISON OF DEXEF PROXETIL POWDER ORAL SUSPENSION VS CEFIXIME POWDER # 9/25/90#
225	"COMPARISON OF DEXEF PROXETIL POWDER FOR ORAL SUSPENSION VS CEFIXIME POWDER FO#R ORAL SUSPENSION" 9/25/90#
226	"COMPARISON OF DEXEF PROXETIL POWDER FOR ORAL SUSPENSION VS CEFIXIME POWDER#9/25/90#
227	"COMPARISON OF DOXEF PROXETIL POWDER FOR ORAL SUSPENSION VS CEFIXIME POWDER FO#R ORAL SUSPENSION IN THE TREATM'? OF
228	ACUTE SUPPURATIVE OTITIS MEDIA IN INFANTS# AND CHILDREN" 9/25/90
229	"COMPARISON OF DOXEF PROXETIL POWDER FOR ORAL SUSPENSION VS CEFIXIME POWDER FO#R ORAL SUSPENSION IN THE TREATMENT O
230	F ACUTE SUPPURATIVE OTITIS MEDIA IN INFANT#S AND CHILDREN" 9/25/90
231	"COMPARISON OF DOXEF PROXETIL POWDER FOR ORAL SUSPENSION VS CEFIXIME POWDER FO#R ORAL SUSPENSION IN THE TREATMENT O
232	F ACUTE SUPPURATIVE OTITIS MEDIA IN INFANT#S AND CHILDREN"# #
233	"DOXEF PROXETIL ORAL SUSPENSION DOXEF VS PEN V FOR PHARYNGITIS" 10/19/89# #
234	"DOXEF PROXETIL ORAL SUSPENSION DOXEF VS PEN V FOR PHARYNGITIS" 10/19/89# #
235	"DOXEF PROXETIL ORAL SUSPENSION DOXEF VS PEN V FOR PHARYNGITIS" 10/19/89# #
236	"DOXEF PROXETIL ORAL SUSPENSION DOXEF VS PEN V FOR PHARYNGITIS" 10/19/89# #
237	"DOXEF PROXETIL ORAL SUSPENSION DOXEF VS PEN V FOR PHARYNGITIS" 10/19/89# #
238	"COMPARISON OF ORAL DOXEF PROXETIL ORAL SUSPENSION AND PENICILLIN V POTASSIUM #ORAL SUSPENSION IN THE TREATMENT OF
239	ACUTE STREP PHARYNGITIS/TONSILLITIS IN INF#ANTS AND CHILDREN"
240	"DOXEF PROXETIL ORAL SUSPENSION DOXEF VS PEN V FOR PHARYNGITIS"# #
241	"DOXEF PROXETIL ORAL SUSPENSION DOXEF VS PEN V FOR PHARYNGITIS" 10/19/89# #
242	"COMPARISON OF ORAL CEFPODOXIME PROXETIL ORAL SUSPENSION AND PENICILLIN V POTA#SSIUM ORAL SUSPENSION IN THE TREATME
243	NT OF ACUTE STREPTOCOCCAL PHARYNGITIS/TONS#ILLITIS DUE TO STREPTOCOCCUS PYOGENES"

	IND	ANUM	PART	SDATE	PAT_TRNUM	RPAGE
245	0000033641	26	SD	3/11/91	9155/90/018	6-53
246		26	SD	3/11/91	9155/90/018	6-53
247		26	SD	3/11/91	9155/90/018	6-53
248		26	SD	3/11/91	9155/90/018	6-53
249		26	SD	3/11/91	9155/90/018	6-53
250		26	SD	3/11/91	9155/90/018	6-53
251		26	SD	3/11/91	9155/90/018	6-53
252		26	SD	3/11/91	9155/90/018	6-53
253		26	SD	3/11/91	9155/90/018	6-53
254		26	SD	3/11/91	9155/90/018	6-53
255		26	SD	3/11/91	9155/90/018	6-53
256		26	SD	3/11/91	9155/90/018	6-53
257		26	SD	3/11/91	9155/90/018	6-53
258		26	SD	3/11/91	9155/90/021	54-100
259		26	SD	3/11/91	9155/90/021	54 - 100
260		26	SD	3/11/91	9155/90/021	54 - 100
261		26	SD	3/11/91	9155/90/021	54 - 100
262		26	SD	3/11/91	9155/90/021	54 - 100
263		26	SD	3/11/91	9155/90/021	54 - 100
264		26	SD	3/11/91	9155/90/021	54 - 100
265		26	SD	3/11/91	9155/90/21	54 - 100
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245	"DOXEF PROXETIL ORAL SUSPENSION DOXEF VS PEN V FOR PHARYNGITIS"# #
246	"DOXEF PROXETIL ORAL SUSPENSION DOXEF VS PEN V FOR PHARYNGITIS"# #
247	"DOXEF PROXETIL ORAL SUSPENSION DOXEF VS PEN V FOR PHARYNGITIS"# #
248	"CEFPODOXIME PROXETIL ORAL SUSPENSION DOXEF VS PEN V FOR PHARYNGITIS"# #
249	"COMPARISON OF ORAL DOXEF PROXETIL ORAL SUSPENSION AND PENICILLIN V POTASSIUM #ORAL SUSPENSION IN THE TREATMENT OF
250	ACUTE STREP PHARYNGITIS/TONSILLITIS IN INF#ANTS AND CHILDREN"
251	"COMPARISON OF ORAL DOXEF PROXETIL ORAL SUSPENSION AND PENICILLIN V POTASSIUM #ORAL SUSPENSION IN THE TREATMENT OF
252	ACUTE STREP PHARYNGITIS/TONSILLITIS IN INF#ANTS AND CHILDREN"
253	"CEFPODOXIME PROXETIL ORAL SUSPENSION CEFPODOXIME VS PEN V FOR PHARYNGITIS"# #
254	"COMPARISON OF ORAL DOXEF PROXETIL ORAL SUSPENSION AND PENICILLIN V POTASSIUM #ORAL SUSPENSION IN THE TREATMENT OF
255	ACUT STREP PHARYNGITIS/TONSILLITIS IN INFA#NTS AND CHILDREN"
256	"DOXEF PROXETIL ORAL SUSPENSION DOXEF VS PEN V FOR PHARYNGITIS"# #
257	"DOXEF PROXETIL ORAL SUSPENSION DOXEF VS PEN V FOR PHARYNGITIS"# #
258	"COMPARISON OF ORAL DOXEF PROXETIL ORAL SUSPENSION AND PENICILLIN V POTASSIUM #ORAL SUSPENSION IN THE TREATMENT OF
259	ACUTE STREPTOCOCCAL PHARYNGITIS/TONSILLITI#S IN INFANTS AND CHILDREN"
260	"COMPARISON OF ORAL DOXEF PROXETIL ORAL SUSPENSION AND PENICILLIN V POTASSIUM #ORAL SUSPENSION IN THE TREATMENT OF
261	ACUTE STREPTOCOCCAL PHARYNGITIS/TONSILLITI#S IN INFANTS AND CHILDREN".
262	"DOXEF PROXETIL ORAL SUSPENSION DOXEF VS PEN V FOR PHARYNGITIS" 10/19/89# #
263	"DOXEF PROXETIL ORAL SUSPENSION DOXEF VS PEN V FOR PHARYNGITIS" 10/19/89# #
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266	"DOXEF PROXETIL ORAL SUSPENSION DOXEF VS PEN V FOR PHARYNGITIS" 10/19/89# #
267	"DOXEF PROXETIL ORAL SUSPENSION DOXEF VS PEN V FOR PHARYNGITIS" 10/19/89# #
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	IND	ANUM	PART	SDATE	PAT_TRNUM	RPAGE
270	0000033641	26	SD	3/11/91	9155/90/021	54 - 100
271		26	SD	3/11/91	9155/90/021	54 - 100
272		26	SD	3/11/91	9155/90/021	54 -100
273		26	SD	3/11/91	9155/90/021	54 -100
274		26	SD	3/11/91	9155/90/021	54 - 100
275		26	SD	3/11/91	9155/90/021	54 - 100
276		27	NS	5/ 2/91		1
277		28	NS	6/21/91		1
278		28	NS	6/21/91		14
279		29	NS	8/30/91		3
280		30	NS	10/16/91		2
281		31	MD	11/12/91		COMPONENTS, COMPOS
282		32	NS	11/18/91		2
283		32	NS	11/18/91		16
284		32	NS	12/11/91		2
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270	"DOXEF PROXETIL ORAL SUSPENSION DOXEF VS PEN V FOR PHARYNGITIS" 10/19/89# #
271	"DOXEF PROXETIL ORAL SUSPENSION DOXEF VS PEN V FOR PHARYNGITIS" 10/19/89# #
272	"DOXEF PROXETIL ORAL SUSPENSION DOXEF VS PEN V FOR PHARYNGITIS" 10/19/89# #
273	"DOXEF PROXETIL ORAL SUSPENSION DOXEF VS P V FOR PHARYNGITIS"# #
274	"DOXEF PROXETIL ORAL SUSPENSION DOXEF VS PEN V FOR PHARYNGITIS" 10/19/89# #
275	"DOXEF PROXETIL ORAL SUSPENSION DOXEF VS PEN V FOR PHARYNGITIS" 10/19/89# #
276	"COMPARISON OF DOXEF PROXETIL POWDER FOR ORAL SUSPENSION VS CEFIXIME POWDER FO#R ORAL SUSPENSION IN THE TREATMENT O
277	F ACUTE SUPPURATIVE OTITIS MEDIA IN INFANT#S AND CHILDREN" 9/25/90
278	"COMPARISON OF DOXEF PROXETIL POWDER FOR ORAL SUSPENSION VS CEFIXIME POWDER FO#R ORAL SUSPENSION IN THE TREATMENT O
279	F ACUTE SUPPURATIVE OTITIS MEDIA IN INFANT#S AND CHILDREN" 9/25/90
280	"COMPARISON OF DOXEF PROXETIL POWDER FOR ORAL SUSPENSION VS CEFIXIME POWDER FO#R ORAL SUSPENSION IN THE TREATMENT O
281	F ACUTE SUPPURATIVE OTITIS MEDIA IN INFANT#S AND CHILDREN" 9/25/90
282	"EVALUATION OF THE EFFECTS OF A STANDARD FDA HIGH-FAT BREAKFAST ON THE RATE AN#D EXTENT OF CEFPODOXIME PROXETIL FLA
283	VORED GRANULES#
284	"COMPARISON OF THREE ANTIBIOTIC REGIMENS FOR THE TREATMENT OF ACUTE PHARYNGOTO#NSILLITIS IN CHILDREN DUE TO GROUP A
285	BETA-HEMOLYTIC STREPTOCOCCUS 10/16/91#
286	"COMPONENTS, COMPOSITION, MFG AND PACKAGING INFO STABILITY AND CONTROL"# #
287	"COMPARISON OF THREE ANTIBIOTIC REGIMENS FOR THE TREATMENT OF ACUTE PHARYNGOTO#NSILLITIS IN CHILDREN DUE TO GROUP A
288	BETA-HEMOLYTIC STREPTOCOCCUS" 10/16/91#
289	"COMPARISON OF THREE ANTIBIOTIC REGIMENS FOR THE TREATMENT OF ACUTE PHARYNGOTO#NSILLITIS IN CHILDREN DUE TO GROUP A
290	BETA HEMOLYTIC STREPTOCOCCUS" 10/16/91#
291	"COMPARISON OF THREE ANTIBIOTIC REGIMENS FOR THE TREATMENT OF ACUTE PHARYNGOTO#NSILLITIS IN CHILDREN DUE TO GROUP A
292	BETA-HEMOLYTIC STREPTOCOCCUS" 12/11/91#
293	

	IND	ANUM	PART	SDATE	PAT_TNUM	RPAGE
295	0000033641	33	NS	12/13/91		3
296		35	NS	1/10/92		2
297		35	NS	1/10/92		24
298		37	NS	1/21/92		2
299						
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295	"BICEQUIVALENCE STUDY OF CEFPODOXIME PROXETIL FOR ORAL SUSPENSION COMPARISON OF PRODUCT-BATCH AND BIOBATCH ORAL SU
296	SPENSIONS" 12/13/91#
297	"COMPARISON OF THREE ANTIBIOTIC REGIMENS FOR THE TREATMENT OF ACUTE PHARYNGOTO#NSILLITIS IN CHILDREN DUE TO GROUP A
298	BETA-HEMOLYTIC STREPTOCOCCUS" 9/25/90#
299	"COMPARISON OF THREE ANTIBIOTIC REGIMENS FOR THE TREATMENT OF ACUTE PHARYNGOTO#NSILLITIS IN CHILDREN DUE TO GROUP A
300	BETA-HEMOLYTIC STREPTOCOCCUS" 9/25/90#
301	"COMPARISON OF THREE ANTIBIOTIC REGIMENS FOR THE TREATMENT OF ACUTE PHARYNGOTO#NSILLITIS IN CHILDREN DUE TO GROUP A
302	BETA-HEMOLYTIC STREPTOCOCCUS" 10/16/91#
303	

DOXEF™ Granules

RED 1-9-90 Amendment 004
Submitted Protocol P/1140/0032 Part 6 for Jacobs

RED 1-30-90 Amendment 005
Submitted Part 6 Protocol M/1140/0013 Cornay, M1140/0020 Foulds, Maderazo, Pastor, Wiederhold, M/1140/0027 Chiulli, Hedrick, Kline, Mendelson, Wiederhold, M/1140/0028 Foulds, Frenkel, Revisions M/1140/0020 Bocchini, Gooch, Hooper, McCarty and listed subinvestigators

RED 3-3-90 Smrnfsmy 006
Request a meeting to demonstrate what we are now capable of providing electronically

JRB 2-20-90 Amendment 007
Part 6, Protocol M/1140/0020 Goudarzi, Olk, M1140/0028 Olson

JRB 3-9-90 Amendment 008
Part 6 M/1140/0020 Cohen, Nahata, ST111, Revisions M1140/0020 Rodriguez and new subinvestors. TRs 7228/89/019 Ames Assay, TR 7224/90/009 Oral Rat

RWL 3-20-90 Amendment 009
Request a meeting to demonstrate CANDAR for NDA

JRB 4-3-90 Amendment 010
Part 6 M/1140/0013 Feinberg, M/1140/0020 Feinberg, Straub and subinvestigators

RWL 4-6-90 Amendment 011
Confirming meeting for 4-19-90 at 10:00 a.m. per telephone conversations

JAE 4-20-90
Request a "PRE_NDA meeting" to discuss scope of NDA

RWL 5-16-90 Amendment 14
Submitted prototypes of data displays for screens re CANDA per request

JAE 5-23-90 A#15
Submitted additional info on the Statistical Analysis plans in preparation for Pre NDA filing meeting on 6-18-90

JAE 5-30-90 A#16
Submitted Safety Report re a nine month old female who received four times dosage with no serious adverse effects

JAE 7-10-90 A#18
Submitted Safety Report re event which was serious and unexpected from Japan

JAE 7-11-90 Amendment #19
Submitted Part 6 M/1140/0020 Smith

IND 33,641

DOXEPᵒ Flavored Granules

RWL 7-18-90
Request comments re M/1140/0043, 0044 & 0045 prior to formal submission from Dr. Susan Alpert per request

CPE 7-25-90 Amendment #020
Submitted Safety Reports which were serious and unexpected from Japan where marketed

JAE 8-3-90 Amendment #021
Submitted modified tables for review and a brief summary of telephone conversation of 7-17-90

JAE 8-7-90
Submitted several journal articles we failed to include with our 7-18-90 letter

JAE 4-23-90 A#012
Submitted Part 6/1-16 Protocol P1140/0035, Bluestone 6/17-20 & Labeling Page 7/1

JAE 4-30-90 A#013
Submitted Part 6/1-31Protocol M1140/0020, McLinn, Rettig, Tyler & co/inv., Part 7/1 Labeling

JAE 5-31-90 A#017
Submitted Part 6/1-14 Protocol M1140/0020, Drehobl, Puopolo, Goldblatt, co/invs. & Part 7/1 Labeling

JAE 9-26-90 A#22
Submitted Part 6/1-73, Protocol M1140/0043, Hedrick, McLinn, Wiederhold, Protocol P1140/0038 Hughes & co/invs, Part 7 Labeling

JAE 10-31-90 A#23
Submitted Part 6 1-48, Protocol M1140/0020 Cohen co/inv., Protocol M1140/0043 Dajani, Neiderman, Mendelman, Shelton,Shirin, & Change in Protocol M1140/0038 Page 49

JAE 11-5-90
Please submit our tradename to FDA's Labeling and Nomenclature Committee for an assessment of our tradename

JAE 12-17-90 A#24
Submitted Annual Report

JAE 12-18-90 A#25
Submitted Protocol M1140/0043 Bowerl-4 & subs, Simoes 5-12, Bluestone 12-18, list of subs

VANTIN ® Flavored Granules IND 33,641 (name changed from Doxef 4-27-92)

1-11-91 Comments re 11-6-90 meeting re proposed CANDA - Submission date for the NDAs is 3-29-91

3-11-91 A#026 Submitted Part 6/1-5 Felder added sub for Bluestone P/1140/0035, 6/5-53 TR 9155/90/018, 6/54-100 TR 9155/90/021

5-2-91 A#27 to add Feinberg to Protocol M1140/0043 Part 6/1-4

5-7-91 A#001 Addendum includes Amendment #1 for Dennis L. Swartout for Protocol M1140/0028 which was inadvertantly omitted from A#001

5-28-91 Declare the trade name DOXEF to be unacceptable because of safety and and another name should be proposed

6-21-91 A#28 Submitted Howie to Protocol M/1140/0043 1-13 & subs and Chanin 14-21 same protocol

8-30-91 A#029 Submitted Page 1-15 Protocol P/1140/0058 Peters 16-18, Labeling 19-20

10-16-91 A#030 Submitted Pages 2-37 Protocol M/1140/0054 Gooch & subs 38-77, Labeling 78-79

11-12-91 A#31 Submitted Part 7/1-44 Chemistry/Mfg/Control

11-18-91 A#32 Submitted New investigator Stephan Arcnoff & co's 1-14 Protocol M/1140/0054, 15-39 Blumer & co

12-11-91 A#33 Submitted New Protocol M/1140/0059, Investigarot Adna S. Dajani and Sub/Inv Mirta Soler, Jennie Andersen, Chandra Edwin, Protocol change (amendment 1) can be found on page 38a of this submission, part 7 - labeling is provided for protocol M/1140/0054 and also applies to the protocol M/1140/0059

12-13-91 A#33 Submitted new protocol P/1140/0039, pages 1 - 14, investigator Albert J. Diets

1-3-92 A#34 (corrected amendment No.) Submitted new protocol P/1140/0039, pages 1 - 14, investigator Albert J. Diets

1-10-92 A#35 Protocol amendment, new investigators M/1140/0054 - multicenter study, Investigator Richard F. Jacobs, Sub/Inv Gordon E. Schutze, Joseph Elser, Toni Darville, Nancy Tucker, Investigator Michael E. Pichichero, and Sub/Inv Frank A. Disney, John L. Green, Anne B. Francis, Steven M. Rarsocci, Marie Lynd, Gordon C. Wood

1-17-92 A#36 Submitted Safety Report - Medical Event: Pancolitis

1-21-92 A#37 Submitted protocol amendment, new investigator M/1140/0054, William Rodriguez, subinvestigators, Waheed N. Khan, Om P. Chhabra, Tahir Sait, Arthur Guarinello, Alan W. Smith. Protocol Change P/1140/0039 (amendment 1) is necessary for protocol instructions regarding constitution of the investigational lot (lot 26,255) made in Belgium to be consistent with the final labeling of the product. Part 7 - Labeling - pages 22-24

2-21-92 A#38 Submitted Annual Report - time period from July 7, 1990 - July 6, 1991

5-14-92 A#39 - Information amendment to include the following clinical technical reports: TR 9155/90/33, TR 9155/90/001, TR 9155/91/006, TR 9155/90/37

7-24-92 A#40 - Submitted Safety Report

APPENDIX C-4

Summary of Correspondence During NDA for VANTIN Granules (Formerly called DOXEF Granules)

Cefpodoxime Proxetil Flavored Granules (DOXEF®) NDA 50-675 (Name changed to TUCEF™ 9-91) (Name changed to VANTIN® 4-27-92)

8-29-91 Submitted original NDA
- 9-29-91 FDA acknowledged receipt
- 4-11-91 Filing date will be 6-29-91
- 8-13-91 Received fax of deficiencies in the CMC sections
- 8-15-91 Received a copy of the Microbiology Section Review
- 3-6--92 Extension of FDA review time to 6/29/92
- 8-7-92 NDA 50-674 & 50-675 are approved effective as of the date of this letter

4-16-91 Notifies FDA that we will deliver equipment to them that will be used to review the Chemistry-Manufacturing-Control sections of the NDA (optical drive, etc.) on 4-18-91

5-14-91 Providing samples for assay methods validation as requested by FDA

5-20-91 Submitted corrected pages for original NDA
- 5-21-91 Ack'd receipt

5-29-91 Submitted components and values of the workstation delivered to Dr. Susan Alpert on 5-2-91

6-19-91 Submitted revised pages for Volume 1.1 index
- 6-20-91 Ack'd receipt

7-11-91 Submitted TUC personnel and issues for discussion for 7-17-91 meeting
- 7-11-91 Ack'd receipt

7-26-91 Submitted 5 Protocols prior to beginning testing program per meeting of 7-17-91
- 7-30-91 Ack'd receipt
- 8-29-91 FDA will accept release of bulk on basis of Sankyo assay. TUC must perform all tests on first 8 lots and every 10th lot thereafter

9-13-91 A#1 Submitting a safety update (1st submission with new name TUCEF™) 5 volumes

9-16-91 Mary still has this submission
- 10-3-91 Consider a major amendment and have determined t hat 180 additional days will be required for its review 3-14-92 is new date

10-4-91 Providing with two copies of domestic pivotal study protocols and their corresponding list of investigators per request

11-11-91 Submitted Environmental Assessment which Sankyo prepared for inclusion in its DMF

12-13-91 - The status of Case 906 and Case 913, Protocol M/1140/0013 has been revised due to new information. The organisms from both individuals were susceptible. Both cases received cefpodoxime and were considered bacteriologic cure.

12-19-91 Submitted revised Microbiology Section in the package insert as suggested in FDA fax dated 8/14/91 except for retaining "(including penicillinase- and non-penicillinase producing strains)"

1-15-92 A#2 Submitted Safety Report, safety info is summarized for the reporting period of Oct 1, 1990 (NDA cut off date) to July 7, 1991)
1-16-92 Acknowledged Receipt

1-30-92 Submitted draft CFR monographs

2-10-92 - Per telephone last week we sent the TasoHaas column (Number 8TLM4987) for validation of T/A 1676

2-12-92 Submitted A#3 Environmental Assessment
2-13-92 Acknowledged receipt

2-18-92 - Submitted the following corrections that have been made to TR 9155-90-018 - page 2 Conclusions: (moved from first to third bullet) and page 45 Conclusions (moved from first to third bullet)

3-5-92 - Submitted Technical Report #7215/92/005 entitled "Bioequivalence Study of Clinical Lot and Production Lot of Cefpodoxime Proxetil Flavored Granules (Protocol P/1140/0039)

3-6-92 - Provided responses to the deficiencies in the Control/Manufacturing section of the NDA

3-25-92 -Addendum to A#3, per request of Dr. Phillip Vincent, all raw data is submitted in 7 volumes. Only one archival copy will be submitted to each NDA per telephone conversation with Ms Peter Dionne

3-31-92 - We are revising the Microbiology section of the cefpodoxime proxetil tablets and oral suspension insert to include the following statement in the second sentence of the first paragraph: "Cefpodoxime is highly stable in the presence of beta-lactamase enzymes. As a result, many organisms resistant to penicillins and some cephalosporins, due to the presence of beta-lactamases, may be susceptible to cefpodoxime.

4-8-92 - Submitted CMC section of Item 3 "Chemistry-Manufacturing-Cjontrol"

4-28-92 - CANDA equipment has been removed from the office of Mr. Peter Dionne, HFD-520

4-30-92 - A#4 - Minor revisions should be made in Item 8, production lot size, adjustment in the excipient ranges for the amount of opadry applied, change in order of mixing binder solution components, identification debossed on tablet and removal of in-process control test for film coated tablet moisture

4-30-92 - FDA Acknowledged receipt

5-28-92 A#5 - Submitted updated stability data for VANTIN Oral Suspension to request an 18 month expiration dating stored at room temperature. A meeting has been scheduled for June 4 with Peter Dionne, PhD and Mr. Carmen DeBellas to discuss this data.

6-2-92 - We are in receipt of the FDA May 7, 1992 review of the Environmental Assessments for VANTIN® Tablets, NDA 50-674 and VANTIN® for Oral Suspension NDA 50-675 and have listed the comments from the FDA, and our responses. This information responds to all deficiencies listed in the May 7 review.

6-9-92 - Provided the following information in response to requests made from June 5, 1992 telephone discussion with Jeff Mehring, Upjohn: 1) Calculations pertaining to enviromental concentrations of released substances are shown in Section 8. Thise includes a calculation for the MEEC. 2) An additional summary table for environmental parameters.

6-15-92 A#6 Submitted information which was presentated at meeting of June 4, 1992 botween TUC and the FDA.

6-17-92 - Ack'd receipt

6-15-92 - Submitted revisions in the package insert for VANTIN Tablets and Oral Sluspension as requested by the FDA review dated March 23, 1992.

6-16-92 - Notified FDA that two submissions to the New Drug Applications had misnumbered two amendments: Amendment No. 4 - dated April 30, 1992 - should be Amendment No. 5 and Amendment No. 5 - dated May 28, 1992 - should be Amendment No. 6

6-17-92 - Ack'd receipt

6-16-92 - Submitted changes of Technical Report #39155-90-021 (Protocol M/1140/0027). This report is located in Volumes 8.9 and 8.10 (overall Volumes 1.13 and 1.14) of NDA 50-675.

6-17-92 - Ack'd receipt

6-23-92 - Submitted inserts for distribution in countries other than the United States per FDA request

6-23-92 - Letter to Jerry Abramson, Ph.D, FDA, reference to Item#1, Sankyo has not been assigned a DMF number by FDA

6-30-92 - Submitted a copy of the cefpodoxime proxetil Environmental Assesment which may be released under Freedom of Information. This fulfills the commitment made in our letter dated June 2, 1992.

7-2-92 - Resubmitted a copy of the cefpodoxime proxetil Environmental Assessment which may be released under Freedom of Information. MSDSs in Item 15 have been replaced with itmeized charts

7-13-92 A#7 - Submitted a third safety update for the period July 8, 1991 to June 1, 1992.

7-13-92 - FDA ack'd receipt

7-14-92 - Amendment to June 30, 2992 Environmental Assessment. A MEEC for the fifth year of production has been added as you have requested.

7-23-92 - Resubmitting pages 15 and 16 of the Freedom of Information copy of Upjohn's Environmental Assessment for cefpodoxime proxetil.

7-24-92 - Letter to the FDA granting permission for Dr. Susan Alpert, FDA, to demonstrate our CANDAR system at the Pharmaceutical Manufacturers Association meeting on October 26 and 27, 1992.

8-10-92 - Pre-launch promotional materials to be used as soon as possible prior to the markett launch of VANTIN® TM Oral Suspension and Tablets which is scheduled for October 1992

8-14-92 - Per August 7, 1992 approval letter for NDA 50-674 abd 50-675, we are submitting twelve final printed inserts (Code 5R2105/1).

8-17-92 - Letter to FDA from Kathleen J. Day enclosing press kit for VANTIN® Oral Suspension and tablets. A copy of final labeling is also provided.

8-31-92 - FDA recommends eliminating use of "extended spectrum" or any comparable claim.

8-19-92 - Letter to FDA from Kathleen J. Day enclosing core introductory promotional materials for VANTIN® Oral Suspension and Tablets to be used at market launch in October 1992.

9-17-92 - FDA comments and/or recommendations on Primmary Care Introductory Ad and Comprehensive Detailer

8-21-92 - Submitted supplement to add statements to the package insert on Clinical Pharmacology - "Effects of Food" and Dosage and Administration

8-27-92 - FDA acknowledged receipt

9-3-92 - Response to questions raised by Dr. Charles Kumkumian, FDA. "Both NF and non-NF Carrageenan gum are listed in the excipients of VANTIN Oral Suspension. Which is used?"

9-17-92 - Letter to FDA that Sankyo, Tokyo, Japan informed us that Amendment 5 was submitted to their Drug Master File on Augusty 28, 1992.

9-29-92 - Per FDA request of August 7, 1992 approval letter, we are supplying the FDA with one bottle and carton for VANTIN Tablets 100 mg and VANTIN for Oral Suspension 100 mg/5 ml.

APPENDIX D

Declaration of Attorney

APPENDIX D

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re	:	U.S. Patent 4,486,425
Issued	:	4 December 1984
To	:	Hideo Nakao, Koichi Fujimoto, Sadao Ishihara, Shinichi Sugawara, Isamu Igarashi
For	:	*7-[2-(2-Aminothiazol-4-yl)-2-(Syn)-Methoxyiminoacetamido]-3-Methoxymethyl-3-Cephem-4-Carboxylates*

Commissioner of Patents and Trademarks
Box Patent Extension
Washington, DC 20231

DECLARATION

Sir:

The undersigned attorney, who has been given Power of Attorney by Sankyo Co. Ltd., which is the Applicant for Extension of Patent Term under 35 USC 156 with regard to U.S. Patent 4,486,425, hereby declares as follows:

1. THAT he is a patent attorney authorized to practice before the Patent and Trademark Office and has general authority from the owner to act on behalf of the owner in this patent matter;

2. THAT he has reviewed and understands the contents of the application being submitted pursuant to 35 USC 156 and 37 CFR 1.740;

3. THAT he believes the patent is subject to extension pursuant to 35 USC 156 and 37 CFR 1.710;

4. THAT he believes an extension of the length claimed is fully justified under 35 USC 156;

5. THAT he believes the patent for which the extension is being sought meets the conditions for extension of the term of patent as set forth in 35 USC 156 and 37 CFR 1.720 if the Commissioner

agrees with the interpretation of the law that Applicant is requesting in paragraph 5(A) of the application for extension.

The undersigned hereby declares further that all statements made herein of his own knowledge are true and that all statements made on information and believe are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any extension of patent term issuing thereon.

7 December 1992
Date

Lawrence T. Welch

APPENDIX E

Certificate of Correction and Maintenance Fee Receipts

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 4,486,425
DATED : December 4, 1984
INVENTOR(S) : Hideo Nakao et al

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title Page, Left Column, under the heading "U.S. PATENT DOCUMENTS" insert
--4,278,793 7/1981 Durckheimer et al.....544/21--.

Column 25, line 43: replace "4.20" with --4.10--.

Column 33, line 28: replace "CH_3e,uns/CH/ $_2$)" with --$CH_3\underline{CH}_2$)--.

Signed and Sealed this
Twenty-fourth Day of September 1985

Attest:
Ruth C. Mason
Attesting Officer

DONALD J. QUIGG
Commissioner of Patents and Trademarks—Designate

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D. C. 20231

PAYOR NUMBER
001933

FRISHAUF, HOLTZ, GOODMAN &
WOODWARD, P.C.
600 THIRD AVENUE - 30TH FLOOR
NEW YORK, NY 10016

RECEIVED
JAN 23 1992

DATE MAILED
01/14/92

196367

FRISHAUF, HOLTZ, GOODMAN and WOODWARD, P.C.

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "status" below. An explanation of the codes appears on the reverse of the Maintenance Fee Statement. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	4,486,425	171	495	----	06/304,988	12/04/84	09/23/81	08	NO	PAID

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

ITM NBR	ATTY DKT NUMBER
1	81597

DIRECT THE RESPONSE TOGETHER WITH ANY QUESTIONS ABOUT THIS NOTICE TO:
COMMISSIONER OF PATENTS AND TRADEMARKS, BOX M. FEE, WASHINGTON, DC 20231

PTOL-439 (REV. 4-88)

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D. C. 20231

PAYOR NUMBER
001933

FRISHAUF, HOLTZ, GOODMAN &
WOODWARD, P.C.
261 MADISON AVENUE
NEW YORK NY 10016

RECEIVED
FEB 25 1988
FRISHAUF, HOLTZ,
GOODMAN & WOODWARD, P.C.

DATE MAILED
02/18/88

038198

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "status" below. An explanation of the codes appears on the reverse of the Maintenance Fee Statement. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	4,486,425	170	225	----	06/304,988	12/04/84	09/23/81	04	NO	PAID
2	4,487,781	170	225	----	06/410,695	12/11/84	08/23/82	04	NO	PAID
3	4,486,497	170	225	----	06/395,966	12/04/84	07/07/82	04	NO	PAID
4	4,474,733	170	225	----	06/350,048	10/02/84	02/18/82	04	NO	PAID
5	4,482,686	173	450	----	06/538,352	11/13/84	10/03/83	04	NO	PAID

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

ITM NBR	ATTY DKT NUMBER
1	81597
2	80386C
3	82400
4	82105

DIRECT THE RESPONSE TOGETHER WITH PART B OF THIS NOTICE, AND ANY QUESTIONS ABOUT THIS NOTICE TO:
COMMISSIONER OF PATENTS AND TRADEMARKS, BOX M. FEE, WASHINGTON, DC 20231

PTOL-439 (REV. 1-86)

PART A

APPENDIX F

Declaration of Hiroshi Oda
(Original to be Filed upon Receipt)

APPENDIX F

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re	:	U.S. Patent 4,486,425
Issued	:	4 December 1984
To	:	Hideo Nakao, Koichi Fujimoto, Sadao Ishihara, Shinichi Sugawara, Isamu Igarashi
For	:	*7-[2-(2-Aminothiazol-4-yl)-2-(Syn)-Methoxyiminoacetamido]-3-Methoxymethyl-3-Cephem-4-Carboxylates*

Commissioner of Patents and Trademarks
Box Patent Extension
Washington, DC 20231

DECLARATION OF HIROSHI ODA

Sir:

I, Hiroshi Oda, state and declare as follows:

1. I am Director, Patent Department, Sankyo Company Limited (Sankyo), of Tokyo Japan.

2. I make this declaration in support of the application for extension of the above-identified US patent 4,486,425, being submitted concurrently herewith pursuant to 35 USC 156 and 37 CFR 1.740.

3. Sankyo Company Limited is the sole assignee of US patent 4,486,425.

4. Due to a misunderstanding between Sankyo and Sankyo's US licensee, The Upjohn Company of Kalamazoo, Michigan, Sankyo was not aware that an extension application had not been filed for this patent until they received a telefax from Upjohn on December 4,1992.

5. Sankyo intended to file an extension application for the above identified patent according to the provisions of 35 USC 156 and 37 CFR 1.740 and the failure to file such an application until now was completely unintentional.

6. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and believe are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any extension of patent term issuing thereon.

SANKYO COMPANY, LIMITED

December 7, 1992
Date

Hiroshi Oda
Signature

Hiroshi Oda
Director
Patent Department